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## URETERAL STRICTURE—REPORT OF 100 CASES<sup>1</sup>

By GUY L. HUNNER, M.D., F.A.C.S., Baltimore

(From the Gynecological Department of The Johns Hopkins University and Hospital)

Ureteral stricture or narrowing of the ureteral lumen due to intrinsic inflammatory changes in the ureteral wall is a disease far more common and of vastly greater importance than the literature or our previous experience has led us to believe.

In a preliminary paper read before the Genitourinary Section of the New York Academy of Medicine in January, 1916,<sup>2</sup> the author reported 50 cases of ureteral stricture occurring in his practice up to November 1, 1915. In the same period of 13 years of practice there were records of 49 cases of nephrectomy for tuberculosis and 39 cases of stone in the ureter. In the 18 months since November 1, 1915, or since becoming alive to the importance of the subject, and since looking for stricture, talking stricture, and having confrères refer suspected cases for diagnosis and treatment, the author has seen more than 100 additional cases.

This paper will deal in a statistical manner with the first 100 cases only, although the general conclusions will be based on an experience with over 150 cases, and a few of the illustrations will be of recent cases not in the first 100 but showing points of particular diagnostic interest.

*Etiology.*—Up to within the past few years most of the literature on this subject has been devoted to the so-called congenital stricture of the ureter.<sup>3,4</sup>

Kelly<sup>5</sup> anticipates our more modern literature of the subject by stating that "Strictures are caused by an inflammation in the ureteral walls produced by the commoner pyogenic cocci, by the gonococcus, and by the tubercle bacillus. The commonest form of inflammation is that due to the tubercle bacillus, and the rarest in my experience in women is due to the gonococcus."

Garceau,<sup>6</sup> on the other hand, says, after reviewing the literature, and in the light of his own experience, "The chief cause of fibrous stricture is gonorrheal infection."

Furniss<sup>7</sup> took issue with the prevailing opinion that most ureteral strictures are congenital in origin, and from a study of his cases concluded that infection plays the important part in the production of ureteral stricture. He thinks that the

<sup>2</sup> Bottomley: Certain Congenital Strictures of the Ureter. *Annals of Surgery*, 1910, LII, 597.

<sup>4</sup> Eisendrath: Congenital Stenosis of the Ureter. *Surg., Gyn. & Obstet.*, 1911, XII, 533.

<sup>5</sup> Stricture of the Ureter. *Jour. Amer. Med. Assn.*, 1902, XXXIX, 363.

<sup>6</sup> Ureteritis in the Female. *Amer. Jour. Med. Sci.*, 1903, CXXV, 284.

<sup>7</sup> *Jour. Amer. Med. Assn.*, 1912, LIX, 2051.

<sup>1</sup> Paper read before The Johns Hopkins Hospital Medical Society, May 7, 1917.

<sup>2</sup> Stricture of the Ureter, Excluding Tuberculosis and Calculus; Report of Fifty Cases. *New York Med. Jour.*, July 1, 1916.



infiltration in the ureter is the result of an acute hematogenous infection of the kidney, which often persists as a pyelitis, ureteritis, or secondary cystitis.

Furniss quotes Sugimura<sup>8</sup> as having studied the lower end of the ureters in the bodies of 25 patients, who had had cystitis but had died of other causes. He found changes of an inflammatory type in the submucosa and muscularis and was of the opinion that the infection extended through the lymphatics and not along the mucosa.

Necker<sup>9</sup> exhibited before the Deutsche Gesellschaft für Urologie, at the Congress in Vienna in September, 1911, pyelograms of cases of pyelitis, all showing some dilatation of the renal pelvis, and in explanation said that they were cases of ureteral obstruction with secondary infective hydronephrosis.

Kelly and Burnam,<sup>10</sup> speaking of traumatic stricture, voice our common experience in stating that "Traumatic stricture of the vesical end of the ureter following the injuries of labor and of surgical operations especially the Wertheim operation for cancer of the cervix uteri, is quite common. As a rule, the trauma has so interfered with the blood supply of the organ that there are lateral necrosis, a continuous leakage of the urine, and ureterovaginal fistula. The spontaneous healing of such a fistula, almost invariably, means stricture."

Gun-shot and stab-wound injuries are rare. Morris<sup>11</sup> collected reports on 5 such injuries. Figure 1 shows a stricture resulting from gun-shot injury and giving rise to symptoms 8 years after the injury.

Severe traumatic accidents are rarely the cause of stricture, as one would naturally conclude after consideration of the anatomy of this long flexible organ, well protected along the spine and attached at either end to a movable organ. Any accident severe enough to rupture the kidney or bladder or to crush the bony pelvis might well result in ureteral stricture, but the history would be such as to suggest the etiology in a case of this nature.

Syphilis should be kept in mind as a possible cause of ureteral stricture.<sup>12</sup>

Ureteritis cystica may cause ureteral obstruction from the large size of some of the cysts, but this condition, although probably of inflammatory origin, cannot be classified as ureteral stricture.<sup>13</sup>

Gynecologists might question the possible relationship between infected cervical glands and ureteral stricture. As we shall learn later, the vast majority of these strictures occur in the broad ligament region and it is only natural that we should suspect the cervix as having a possible causal relationship.

It is probable that ureteral stricture occurs more frequently in women than in men, and one is inclined to attribute this to the infections incident to childbirth. Opposed to this theory is the fact that in a considerable proportion of cases the symptoms of stricture begin in childhood or occur in women who have never married and in whom we have no reason to suspect a gonorrheal infection. Our failure to recognize the disease in both sexes has undoubtedly been due to our ignorance of its frequency and consequently to a failure to look for the lesion.

Although I have not seen any reason in any individual case for attributing ureteral stricture to a cervical infection, I have become suspicious of the etiological relationship between focal infections and certain cases of cervicitis. We have a type of urethral inflammation in which the vulva and para-urethral glands are inflamed and the patient has an inflamed cervix furnishing a considerable amount of leucorrhea. This type of inflammation is particularly likely to occur in adult maiden women, who show no other evidence and give no history of onanism or of gonorrheal infection. Time will demonstrate, I believe, that the group of inflammatory foci in the pelvis are secondary to a distant common focus of infection.

The frequent association of ureteral stricture and venous phleboliths in the immediate neighborhood speaks for a common origin for the inflammatory process resulting in the two conditions, and suggests that some of these infections may have originated in the genital tract.

While we must admit the possibility and probability of any of the foregoing factors playing a rôle in the etiology of certain ureteral strictures, I am firmly convinced that the majority of ureteral strictures, excluding those of tuberculous origin, should be classified as simple, chronic, stricture, and that they have their origin in an infection carried to the walls of the ureter from some distant focus such as diseased tonsils, sinuses, teeth, or gastro-intestinal tract.<sup>14</sup> This conception of stricture postulates that in the majority of cases ureteral infiltration is primary, and that the other urinary tract lesions so often associated with stricture, such as stone in the ureter, hydronephrosis, pyelitis, and pyonephrosis, are secondary.

As reported in my first paper on "Chronic Urethritis and Chronic Ureteritis Caused by Tonsillitis," read before the 1910 meeting of the Southern Surgical and Gynecological Association at Nashville, and as borne out by a fairly wide experience since that time, I have the proof that certain obstinate cases of chronic urethritis, which will not heal under the ordinary methods of treatment carried on over a long period of time, will promptly become absolutely well without further local treatment by getting rid of the distant focus of infection.

In the case of ureteral stricture it will probably take some years of experience before we can claim to have satisfactory

<sup>8</sup> Virchow's Arch. f. path. Anat., October, 1911.

<sup>9</sup> Zeitschr. f. Urol., 1912, III, 464.

<sup>10</sup> Diseases of the Kidneys, Ureters, and Bladder. Appleton, 1914, II, 354.

<sup>11</sup> Surgical Diseases of the Kidney and Ureter, 1901, II, 332.

<sup>12</sup> Proksch: Arch. f. Dermat. u. Syph., 1899, XLVIII, 224.

<sup>13</sup> Carey and Laird: A Peculiar Hypertrophy of the Prostate Accompanied by Ascending Infection and Cysts in the Ureter. Albany Medical Annals, July, 1904.

<sup>14</sup> Hunner: Chronic Urethritis and Chronic Ureteritis Caused by Tonsillitis. Jour. Amer. Med. Assn., LVI, 937, 1911; Treatment of Pyelitis. Surg., Gyn. & Obstet., XV, 444, 1912; Diagnosis and Treatment of Obscure Cases of Pyelitis and Hydronephrosis. International Clinics, 22, IV, 1912.



proof of the above thesis. Not only must we collect a large number of cases similar to Case 7, reported in the above paper, in which symptoms of ureteral stricture began soon after an attack of tonsillitis, but we must have a series of cases of ureteral stricture in which relief fails through a long period of treatments and is then obtained after the distant focus of infection has been discovered and corrected.

I have a few cases which have persistently showed no material improvement in symptoms until after removal of infected tonsils, or teeth, and another list of patients who have been dismissed as well after dilatation of the strictures or after getting rid of the pyelitis by dilatation of the stricture and lavage, and who have returned with their old symptoms after a fresh tonsillitis attack or after undergoing dental work.

*Symptoms.*—Pain is the most universal symptom of ureteral stricture and only in rare cases is it absent. To attempt to draw a pain chart of this affection one would need a diagram of the human frame extending from the diaphragm to the ankles. The most deeply shaded portion of this chart would center in the local area of ureteral inflammation, or in other words in the broad ligament region deep in the pelvis.

In my preliminary paper above mentioned as read in New York, I said: "It is comparatively rare to have our attention directed to localized symptoms due to the stricture. The patient usually complains of pain in the kidney region or of bladder symptoms or of both, and the stricture is found in the attempt to fathom the cause of the symptoms."

This statement was made after a study of my first 50 cases seen at a period when ureteral stricture as an entity was not in mind. Many of those patients came late when the kidney lesion was advanced and overshadowed other conditions. Since making that report and realizing the importance of ureteral stricture, better histories have been obtained, and it is rare to find a patient with stricture who does not complain of a pain or of a nagging discomfort in the site of the ureteral inflammation.

From this center of inflammatory discomfort in the pelvis the pain may radiate in any direction, upward toward the kidney, laterally into the hips or groin region, posteriorly, simulating a sacroiliac joint condition or a sciatica, and downward into the thigh and leg either posteriorly or anteriorly.

Next in frequency to the local ureteral pain is pain in the kidney region. This is probably at times a referred pain from the inflammatory area in the ureter, but it is usually due to overdistension of the pelvis of the kidney.

At times, when the renal catheter is passed and the wax tip and again the wax-bulb impinge upon the tender stricture area, the patient locates the pain in the kidney region. The kidney pain is usually elicited only by injecting the pelvis to overdistension. Frequently we get the history that the patient suffered at first with a more or less constant pain low in the abdomen, and that she later developed intermittent attacks of pain in the kidney region. Early in the patient's history these intermittent kidney attacks may come on only at the menstrual period or on getting the feet wet, or on having some unusual exposure, conditions that would favor the closure

by swelling of an already narrowed area in the ureter. Later the pain in the upper flank or lumbar region may occur at frequent intervals or become as constant as the ureteral pain.

Occasionally the pain occurs first in the kidney region and develops later in the lower abdominal quadrant or region of the ureteral stricture. (See Figs. 2 and 3.)

Actual pain in the bladder occurs only in the exceptional case, and this is probably a referred pain from the kidney or ureter, as it accompanies the severe acute renal attacks simulating stone in the ureter in which there are likely to be both bladder and rectal tenesmus. Figure 4 illustrates such a case in which the two attacks of renal colic were accompanied by bloody urine and were controlled only by repeated hypodermics of morphia.

Discomfort in the bladder and frequency of voiding are not at all uncommon in the intermittent renal attacks, and these symptoms may be present in patients complaining only of the ureteral pain. One of my recent patients, not in the first one hundred, complained chiefly of a nagging desire to urinate.

Miss P., aged 51 years, had had multiple fibroids removed by Dr. Kelly 4 years previously. Three years later she had begun to have bladder symptoms and in September, 1916, she had returned to Dr. Kelly, who had failed to locate the cause. In May, 1917, she consulted me and in addition to her almost intolerable nagging desire to urinate, causing her to void from every hour to 3 hours in the day and to arise many times at night, I found that she complained of a dull pain in the left hip, of a pain high in the left lumbar region, and of a pain extending down the posterior left thigh into the calf of the leg. More recently she had developed an intermittent pain of less severity in the right hip and in the right side of the back. Investigation revealed a normal urine, a stricture of the urethra but a perfectly normal-appearing vesical, trigonal and urethral mucous membrane. The left ureter had such a dense diffuse stricture that I got by only on the third attempt in a series of 7 efforts within 10 weeks. I found a series of 4 dense areas of obstruction in the left ureter within 6 centimeters of the bladder, and that the kidney pelvis held only 6 c. c. The right ureter showed a dense diffuse stricture extending from the bladder to 9.5 cm. above, which could always be dilated; the kidney pelvis held double the normal quantity. Manipulation of the stricture area on either side caused her nagging desire to void, and manipulation of the left ureteral stricture caused pain in the kidney region, hip, and in the calf of the leg.

*Urine examination.*—The urine may be quite negative on repeated careful centrifuging and microscopic search. If there is an associated pyelitis, the urine shows the pathologic features and variations common to that condition. If the urine is not infected we may still find a few leukocytes or a few erythrocytes or both. These may come from an ulcer area at the site of the stricture, or we may find them increased in number after one of the acute kidney attacks, when they probably result from the trauma to the kidney pelvis. Figure 5 illustrates a unique case of symptomless hematuria apparently due to ureteral stricture.

*Fever.*—Chills and fever are common in the cases with urinary infection. A patient with an infection may go for weeks or months without chills or appreciable fever and, indeed, may be in apparently perfect health, or may suffer only from malaise and general depression. When there occurs any condition that



causes the stricture area to close the patient will develop fever (often with chills) pain and general prostration, such as are usually seen in acute pyelitis.

It is important to note that a patient may develop fever even of a high grade without infection of the urine and with only one ureter involved. The urine may be quite normal or there may be only a few erythrocytes. The kidney is enlarged, tender and painful. A few of the patients with sterile urine have shown a slight daily rise of temperature and these are likely to have nausea, headache, or other uremic symptoms.

One patient with a daily rise of temperature of 99° to 100° F. extending over a period of four weeks, and with a leukocytosis of 19,000, falling in the same period to 12,000, had a normal temperature and leukocyte count of 10,000 ten days after tonsillectomy.

Miss M., aged 22, nurse at the Hebrew Hospital, was awakened one Friday morning with a severe cramp-like pain in the right kidney region extending downward and forward to about the pelvic brim region. She had several attacks with severe pain, nausea and vomiting but kept on duty until the following Monday, when she reported to the superintendent of nurses that she could not continue with her work.

The first attack came on at the end of a menstrual period. For two nights before the attack she had been up frequently to void, and she had too frequent voiding up to the time of entering the hospital as a patient.

Drs. Adler and Hirsh were called to see the patient and because of the character and location of the pain and the presence of microscopic blood in the urine, they considered the case one of stone in the kidney or ureter. X-rays were negative and they called me into the case on October 20, the twelfth day of her illness.

Because of a daily rise of temperature to above 99° F. and a leukocytosis of 19,000 with a high percentage of polymorphs, we considered seriously the possibility of an appendicitis, with a high posterior position of the appendix to account for the pain phenomena. The presence of the above signs and symptoms without pus in the urine argued against a kidney lesion. Blood in the urine is not particularly rare in appendicitis. The patient's pain was more pronounced and more prolonged than one usually sees in appendicitis. She was rather stout, and considering the possibility that the X-ray might have missed a stone, I catheterized the kidney with a wax-tipped bougie. This came back without scratch marks. The meeting of the catheter tip with the kidney pelvis caused an increase of the patient's pain which she likened to that which she had had before. The injection of the kidney pelvis also exaggerated her former pain and the pelvis seemed to be rather smaller than normal, returning only 6 c. c. after being dilated to discomfort. This test of the kidney was followed by three days of intense pain instead of the usual few hours of discomfort caused by such an examination. The patient had to be chloroformed several times to control the pain. The temperature conditions and the leukocyte count remained about the same.

In view of the pain phenomena during catheterization and the great increase in pain after the catheterization, I became more convinced of the possibility of ureteral stricture, although there had been no apparent obstruction to the catheter. The possibility of stricture had been in mind from the first, when, on taking the history, I found that the patient had been troubled with her tonsils from time to time all her life, her last definite attack having occurred about 8 months previously. Another factor in favor of ureteral stricture was the presence of a dense stricture of the urethra. The tonsils appeared normal on examination.

One week after the first catheterization I again catheterized, this time using a wax-bulb. Again I could not detect obstruction, but

the bulb must have had a beneficial effect for the patient did not have the severe pain reaction. Again the kidney pelvis seemed rather smaller than normal.

A week later it was time for the patient to menstruate and she was having increased pain in the kidney region. On catheterization with the wax-bulb catheter, I did not detect obstruction, but the wax-bulb, which was made of white wax and olive oil, equal parts, was partially mashed on withdrawal. A test of the kidney pelvis at this time when the patient was about to menstruate and was having increased pain in the kidney region, showed a capacity of 11 c. c. as compared with 6 c. c. on the two former tests. A week later, 5 weeks after the beginning of the patient's symptoms, my wax-bulb was definitely obstructed at a point about 3 cm. after entering the ureter, and on its withdrawal it was so hung in the stricture area that I feared it would be dragged off the catheter. Fortunately I had a bulb of pure wax on this occasion and it returned intact. After this catheterization the patient had a good deal of pain for an hour or two, due to the trauma incident to the dilatation of the stricture of the urethra and of the ureter. There was none of the increase of kidney pain as on former treatments. A few days later I again dilated the ureteral stricture with a wax-bulb of about 4 mm. diameter and then referred the patient to Dr. Lee Cohen for tonsillectomy. Dr. Cohen reported that on superficial examination the tonsils appeared healthy, but at operation they were found to contain large lacunae of free pus.

*Gastro-intestinal symptoms* are common. They are probably of twofold origin, arising either as a central nervous system reflex or as a result of toxic absorption. We see the same phenomena in certain cases of stone in the ureter and in cases of blockage of the ureter from any cause.

The symptoms vary from a slight nausea or aversion to food to the most extreme nausea and vomiting sometimes so persistent that starvation is threatened. Gaseous distention is a frequent symptom. Occasionally there is complaint of rectal tenesmus and desire for stool. Pain just before or during stool is present in some cases, and is probably due to the passing of fecal matter over the tender peritoneum at the site of the ureteral inflammation. In Case 66 (see Fig. 6) the patient learned by experience that it was more agreeable to omit the meal preceding the dilatation and lavage; otherwise she lost it by vomiting. In Case 65 (see Fig. 7) the patient had suffered for a year with repeated attacks of diarrhoea and had lost 40 pounds in weight. Dr. Barker had found that she had an associated achylia gastrica and she had been given the dilute hydrochloric acid. After dilatation of her ureteral strictures her diarrhoeal attacks ceased and she gained 11 pounds in 2 weeks.

Colitis may occur as a result of stricture. I recently referred a patient to Dr. Ernest Gaither because of much pain in the sigmoid region, through the left hip and in the upper flank, together with frequent stools in which she passed mucous casts. After a careful study of her case Dr. Gaither asked me if it could be possible that she was suffering from a ureteral stricture. That this diagnosis had not occurred to me in going over her symptoms was the more remarkable because she was a patient (Case 2) reported in my paper above referred to on chronic urethritis and chronic ureteritis caused by tonsillitis. A urethritis of 2 years' duration had resisted treatment for several months until her infected tonsils were removed. She had remained free from the urethral symptoms

for more than 6 years and had then begun to complain of the colitis which, after Dr. Gaither's suggestion, I found to be due to a dense stricture of the left ureter. Manipulation of the stricture area and injection of the slightly dilated kidney pelvis did away with all of her discomfort on the left side, and her colitis symptoms ceased after the second ureteral dilatation.

*Mental Symptoms.*—One of the remarkable results of this study has been to find that in a patient who may have one normally functioning kidney and only a slight degree of stasis on the opposite side there may supervene mental disturbances, headaches, nausea, fever, and a general picture usually associated with the uremic state. Figures 8 and 9 are from a patient who had a ureteral kink due to a fan-shaped band of adhesions which suspended her sigmoid to the posterior peritoneum just above the pelvic brim region. While in the recumbent position, taking a "rest cure," to many of which she had been subjected during the 20 years of her symptoms, she would take on weight and be comparatively well. As soon as she returned home and attempted to lead a normal busy life, the weight of the sigmoid displaced her ureter and again caused her "spells." These attacks consisted of a fever ranging from 99° to 100° F., malaise, headache, and a slight pain in the left lumbar region. The patient could "taste her fever" and tell by this peculiar reaction just where the thermometer would register within one-tenth of a degree. It is impossible to say what share toxemia played in her mental condition and how much of it was due to the disappointment and worry over her inability to get well. During her first 6 weeks under Dr. Barker's care it was considered essential to keep her in a barred room and have the constant supervision of a nurse.

The urine was quite normal and X-rays of the abdomen were negative. Dr. Barker asked me to investigate the left kidney because of the slight lumbar pain accompanying her attacks. After freeing the adhesions between the sigmoid and the left ureter peritoneum the patient made a prompt and full recovery and wrote me 6 months after the operation that she had gained 22 pounds.

Another case showing marked mental symptoms due to obstruction in one ureter was that of a physician who suffered for about a year with a morbid mental state entirely foreign to his usual buoyant disposition. Delusions and hallucinations worried him daily and, as in the case above reported, suicide became an urgent impulse. He was entirely relieved after Dr. George Walker had dilated a ureteral stricture.

*Morbid Anatomy.*—We have had opportunity to study the stricture macroscopically in about 15 operation cases. The inflammatory area varies from a slight annular thickening in the ureteral wall to a condition of diffuse cartilage-like thickening which may occupy several centimeters of the ureter and form a mass a centimeter in diameter. Multiple annular strictures are not uncommon.

The infiltration may be confined to the ureteral wall or there may be much periureteritis. Often at operation one cannot tell by palpation whether he is dealing simply with a stricture or with a stricture containing a stone.

I have had opportunity to study the stricture microscopically in only 3 cases (Cases 6 and 26) in which resection of the ureter and implantation into the bladder was performed, and in Case 50, in which we did a nephrectomy. The microscopic picture is one of chronic inflammation of all coats of the ureteral wall; the epithelium is changed from the transitional stratified type to a more squamous type and in one of the specimens there was an ulcer with loss of the epithelium.

*Location of the Stricture.*—The stricture is located in the broad ligament region or within 6 cm. of the bladder in by far the greater number of cases. The next most frequent location is at the bifurcation of the internal iliac vessels or about 8 to 10 cm. above the bladder. This is from 3 to 5 cm. below the pelvic brim. In both of these regions we have a group of lymphatic glands and at operation these are sometimes found enlarged.

Contrast these locations with the generally accepted view that ureteral stricture is congenital and occurs at the points of congenital narrowing, namely where the kidney pelvis enters the ureter, at the pelvic brim, and in the bladder wall area.

In the preliminary report on my first 50 cases, 12 were reported as bilateral. Since then in 3 of the 38 cases, reported as monolateral, the patients have returned with stricture on the opposite side. Of the 35 monolateral cases, 20 were on the right and 15 on the left. Of these 65 ureters with stricture the lesion has been located within 6 cm. of the bladder in 56, at the region of the bifurcation of the internal iliacs in 8 cases, and next to the kidney in 1 case.

In my second list of 50 cases, 15 were bilateral; and of the 35 monolateral cases, 22 were on the right and 13 on the left.

Of this second list of 65 ureters the stricture was located in the broad ligament region only, in 51, in the iliac gland region only, in 1, and in both broad ligament and iliac gland region, in 13. In many of the last group of ureters with strictures in both iliac gland and broad ligament regions the wax-bulb could be felt to jump through several stricture areas and it is probable that in these cases of multiple nodes of thickening there was a condition of diffuse stricture.

*Effects of the Stricture on the Upper Urinary Tract.*—Of the utmost interest is the relationship between ureteral stricture and other lesions of the urinary tract. This study has done much to explain the etiology of many urinary tract lesions concerning which we have had erroneous ideas in the past.

The profession has become accustomed to view slight dilations of the pelvis and ureter as secondary to an infection of the urine. It is even held for the early cases with only slight dilatation and sterile urine that the dilatation was due to a previous infection.

This view, so generally held, is well expressed by Braasch: "Any considerable degree of infection involving the renal pelvis and ureter will be followed by dilatation. This dilatation is not caused by mechanical obstruction, but is the result of changes in the tissues and consequent retraction in the walls of the pelvis and ureter. The dilatation may vary from a scarcely



recognizable irregularity of the calyces or ureter to complete destruction of the pelvis. Evidence of an inflammatory process which has once caused dilatation will rarely be entirely obliterated. Such inflammatory changes in the pelvic or ureteral outline may be the only evidence of previous infection. The character and degree of an inflammatory process can often be determined better by means of the pyeloureterogram than by any other method."

*A priori* one would expect the inflammation and infiltration to result in shrinkage rather than in dilatation of the tract.

While conceding that it is possible for the urine to become infected at the same time that the infection, which is to result in the future stricture, is laid in the ureter wall, I think these studies prove conclusively that the usual sequence is focal infection settling in the ureter wall, stricture formation, stasis and secondary infection of the urine.

Although we believe we have demonstrated that most cases of dilatation of the kidney pelvis are due to mechanical obstruction in the form of ureteral stricture, a surprising development has been the fact that many cases of ureteral stricture causing typical symptoms are not associated with a dilated pelvis, and when the pelvis is not dilated, it is often contracted. These patients with contracted pelvis are usually the most sensitive to manipulation and the contracted pelvis is probably explained by assuming that the extremely sensitive stricture area keeps up a constant pain reflex, causing a tonic spasm of the musculature of the tract above. In some cases the urinary analyses, functional test, and pyelograms indicate that the shrunken pelvis is probably due to a secondary chronic interstitial nephritis. (See Fig. 12.)

Pyeloureterograms of these cases show that in some the ureter seems contracted as well as the kidney pelvis (Figs. 10 and 11) and that in others the pelvis is contracted while the ureter is slightly dilated (Figs. 6, 11½, 12 and 13). In some of these cases the pyelogram shows a larger pelvis than one gets by measurements. Figure 11 shows an apparently normal-sized pelvis, but the capacity tests showed a tolerance of about 4 c. c.

In several patients with normal-sized or contracted pelvis when first seen, the general symptoms have improved under repeated dilatations, but the kidney pelvis has in the same time developed a slight hydronephrosis. The probable explanation of this phenomenon is that a tender ulcer in the stricture area has healed under treatment, thus releasing the reflex spasm, but that the stricture is dense enough to keep up partial obstruction in spite of the dilatations.

The 2 groups making up my first and second list of 50 cases, respectively, illustrate strikingly the effects on the upper urinary tract when ureteral stricture is neglected.

The first group of 50 cases consisted largely of patients seen incidentally at a time when ureteral stricture was not being looked for. In general, in this group of cases it is seen that there is a relationship between the lapse of time, increase in the size of the pelvis, and development of secondary infection. As already indicated above, the second group of cases shows many exceptions to this rule.

In the first group of 50 cases there was no report on the condition of the urine in 6 cases. I have notes on cultures from 27 of the remaining 44 cases. In 9 of these the urine was sterile. Of the 17 cases in which there was no mention of cultures, the urine from the kidney was free from leukocytes in 7, and was presumably sterile, which would make 16 out of 44, or over 33.3 per cent of the reported cases, sterile. In 10 of these 17 cases without mention of cultures there was pus in the specimen catheterized from the bladder, and in 7 of these the kidney specimen is also reported as yielding pus; so that possibly all 10 cases were infected.

In the 16 non-infected cases the average age was 38 years, the average duration of symptoms 2½ years, and the average size of the kidney pelvis in 10 of the cases was 19 c. c., 3 of these holding 8, 11, and 12 c. c. respectively, and the others holding from 15 to 30 c. c. In one exceptional case with symptoms of 4 years' duration the pelvis had reached a capacity of 360 c. c. without becoming infected. In 5 cases there was no note on the pelvis capacity.

In the 18 infected cases the average age of the patients was 35 years, the average duration of symptoms was 4 years, and the average capacity of the kidney pelvis in 15 cases in which a record was made, was 98 c. c. In 4 of these 15 cases the pelvis was of normal capacity, 7 to 8 c. c., showing for the 11 dilated cases an average capacity of 130 c. c. In the cases in which both pelvis were dilated the capacity is figured on the larger pelvis only.

In the 18 infected cases of the first group the colon bacillus was grown in 13, in 5 of these from both kidneys. In 4 cases a staphylococcus only was grown, in 1 case a pure typhoid culture was obtained (nephrectomy for large pyonephrosis soon after typhoid fever). In one of the colon bacillus cases *B. coli* was grown from one kidney and a staphylococcus from the other, making 5 cases in which a staphylococcus was grown.

In the second group of 50 cases all were studied bacteriologically. In 11 there was an infection, in 8 with the colon bacillus (4 bilateral), in 1 with a staphylococcus, in 1 with a streptococcus, and in 1 an unidentified organism. Taking into consideration the 4 bilateral infections there were 15 kidneys involved, and only 4 of these showed dilatation, measuring respectively 15, 14, 20, and 15 c. c. Three of the kidneys measured 1.5 c. c. each and the remaining 8 measured 6 c. c. or less.

In this second group of 50 cases, 15 of which showed bilateral stricture, notes were made on the pelvis content of 63 kidneys. Of these, 22 were normal and ranged in size from 6 to 8 c. c., in 8 the capacity was considered less than normal, the pelvis measuring 5 c. c. or less. In 24 kidneys dilatation was demonstrable and if we exclude the two dilated pelvis in Case 65 (see Fig. 7), the remaining 22 pelvis showed an average dilatation of 16 c. c. in marked contrast to the many large pelvis in the first group.

The average age of the patients in the second group at the time of consultation was 34.5 years and the average duration of symptoms was 5.3 years; but if we separate from this group 7 cases of unusual duration averaging 19 years, the average duration of the remaining cases was 2.6 years.

*Influence of Ureteral Stricture on Stone Formation.*—One of the most interesting side-lights on ureteral disease furnished by this study has been the revelation of the probable cause of most ureteral stones. In operating for a ureteral stone and finding it encased in dense infiltration tissue, we have heretofore considered the inflammatory area as due to the irritation of the stone. At present we have abundant evidence to indicate that the stone results from urinary salts being deposited on the inflamed surface of the stricture area.

Every surgeon sees an occasional case in which a minute stone or a nest of minute stones is found encased in a dense stricture area. It is quite evident that such small stones were not formed in the kidney and then stopped in a normal ureter, nor were they formed in a normal ureter. Such small stones could easily be passed entire through a normal ureter.

There can be no doubt that an occasional stone formed in the kidney is caught in a normal ureter. On the other hand, I believe that some stones found in the kidney were originally formed on the site of a ureteral stricture and after sufficient dilatation of the tract above, these stones had floated up into the kidney where they had increased in size. Figures 14 and 15 illustrate 2 such possible cases. Figure 16 illustrates another possible sequence, *viz.*, that a stone forming in a stricture area may develop a pressure above sufficient to force it out of the stricture and into the bladder. In this case the stone was spontaneously passed from the bladder. In Case 23, the patient had suffered with bladder discomfort and incontinence for 9 months. A stone, 15 mm. in diameter, was removed from the bladder. The X-ray revealed another small shadow in the left broad ligament region, and investigation with the wax tip and wax-bulb catheter demonstrated this to be a venous phlebolith, but the patient had 2 strictures in the broad ligament region and a left colon bacillus pyelitis with a kidney content of 21 c. c.

In Case 71 the patient, aged 37 years, had suffered for 8 years with left renal colic, the attacks becoming so severe recently that they required several hypodermics of morphin for their control. The urine was smoky with blood and contained pus and a colon bacillus infection. On passing a catheter prepared with small wax rings at intervals of 5 cm. for locating the possible ureteral stone, and with one large wax-bulb to dilate the ureter, the catheter returned with scratch marks on all the rings within 20 cm. of the tip. The eye of the catheter contained a particle of stone and the large wax-bulb had embedded in its surface about a dozen particles of stone. The patient was completely relieved of her severe colic attacks and subsequently had several dilatations of the stricture area until her symptoms were relieved. She had the contracted type of pelvis, holding but 4 c. c. Scratch marks were never obtained after the first treatment, which seemed to have entirely cleared out the incipient stone formation.

One of the strongest arguments for the relationship between stone formation and stricture is the finding of bilateral symmetrical stricture and a stone in one of these stricture areas, as has occurred in 4 of my cases, 2 of which are illustrated in Figures 17 and 18. A large stone (see Fig. 19d) was removed

from the right broad ligament area in Case 9, 5 years after I had been dilating strictures in the right broad ligament area and iliac gland region and in the left broad ligament region. The obstruction by the right broad ligament stricture and its stone had made a large dilatation of the right ureter in which at operation the stricture at the iliac gland region was seen to form a dense annular narrowing.

O. S. Fowler, of Denver,<sup>16</sup> has called attention to the possible importance of stasis in the etiology of stone formation. He attributes the stasis to a kink in the ureter due to prolapse of the kidney as demonstrated by the method he has done so much to develop of taking pyeloureterograms in the erect posture. Some of his roentgenograms, however, reveal ureters which are dilated below the point of kinking as well as above and I would interpret them as being cases of unrecognized ureteral stricture low in the channel causing a dilatation of the ureter and kidney pelvis, and a prolapse of the heavy hydronephrotic kidney, causing apparent kinks in the upper ureter. I have several cases of stricture of the ureter showing this kidney prolapse and apparent kinking of the ureter, but they all show the ureteral dilatation down to the stricture area as illustrated strikingly in Figures 2 and 3.

*Influence of Ureteral Stricture on the Pyelitis of Pregnancy and of the Puerperium.*—Of my last seven cases of pyelitis developing during pregnancy or soon after delivery, 3 being bilateral, I have been able to demonstrate stricture of the ureter in all but one case. This is probably a much higher percentage associated with stricture than we would find in a larger series. In most of such cases the stricture is probably present before the pregnancy and the added congestion of the tissues after conception sets up a slight hydronephrosis which becomes infected during the pregnancy or immediately after.

Some of the cases of pyelitis of pregnancy due to stricture clear up spontaneously after labor after the congestion and edema incident to pregnancy have disappeared. Others continue as a chronic pyelitis until treated. Undoubtedly most of those cases of pyelitis of pregnancy which clear up spontaneously or after a few irrigations with silver solution do so because a stricture is not present, or because the slight dilatation of the stricture incident to passing an ordinary renal catheter is beneficial.

That a case may clear up spontaneously in spite of ureteral stricture is illustrated by a patient referred by Dr. Barker (Figs. 12 and 13) for attacks of renal colic associated with chills and high temperature. Fourteen years previously Dr. Kelly had been compelled to perform an abortion for this patient because of a bilateral colon bacillus pyelitis. She had no special treatment for the pyelitis, returned home with an infected urine, and had recurring attacks of pyelitis symptoms on the left side during the intervening 14 years and on the right side for 9 years. Examination revealed very dense bilateral strictures with the kidney pelvis smaller than normal; the ureters showed very slight dilatation. The urine contained

<sup>16</sup> Ureteral Obstruction Causing Urinary Stasis; A New Etiology in Kidney Stone, etc. Jour. Amer. Med. Assn., 1914, LXII, 367.

many hyalin and granular casts and a few pus cells which were proved to be coming from the left kidney. There was no infection. It could very well be argued that this patient had no stricture at the time of her pregnancy and that the pyelitis infection resulted in later stricture formation. My experience with such cases leads me to take the contrary view, particularly as she had suffered all her life with tonsillitis, and because she obtained no permanent improvement from ureter stricture dilatations until after the badly diseased tonsils were removed.

*Diagnosis.*—The diagnosis of ureteral stricture depends upon the history, urinary examination, palpation of the abdomen with special reference to the kidney and ureter regions, palpation of the ureters through the vagina or rectum, cystoscopy, catheterization of the ureters by specially prepared catheters, and roentgenography.

The features obtainable from the history have been discussed above under the section on symptoms. Experience has taught that we should suspect stricture in any patient complaining of obscure abdominal symptoms, particularly in the lower abdomen and accompanied by referred pain in the hips and thighs. In addition we usually find that the patient has a history or shows evidence of tonsillitis, sinusitis, or bad teeth.

After a relatively wide experience in the diagnosis of such obscure cases I have learned to lay a good deal of stress upon a history of previous abdominal or pelvic operations from which the patient has failed to obtain relief. In the second group of 50 cases 34 operations had been done, 7 of which seemed to have been necessary and 27 unnecessary and not followed by relief. Four of the patients had each had 3 operations without relief from the original symptoms. A more recent patient, 36 years of age, with bilateral stricture, had spent a good portion of the previous 18 years in hospitals, having been submitted to 8 operations, 7 of them abdominal. Figures 10, 11, 11½, 15, 20, 21, 22, 23, and 35 illustrate cases of patients who had been operated upon previously without relief from the chief symptoms.

Of course one cannot judge accurately as to what past operations may have been necessary, and we must keep in mind the frequency of ureteral stricture and the possibility that it may have been present with appendicitis, gall-stones, floating kidney, intestinal adhesions, ovarian disease, uterine misplacements, or any of the numerous lesions for which the former operations were done. Three of the above 27 operations listed as unnecessary were performed by myself, 2 for appendicitis, in which a note was made at the operation that the appendix appeared normal, and one for relaxed vaginal outlet and cystocele. In this last case (No. 58) pus and blood were present in the urine and were attributed to a severe trigonitis which in turn was supposed to be due to the cystocele. The patient complained chiefly of a nagging pain in the left broad ligament region, frequency of micturition, and partial incontinence. With the cystocele operation we puckered her sphincter muscle region and cured her incontinence, but she experienced no other relief from the operation and a year later we found that her symptoms of left sided pain and pollakiuria were asso-

ciated with bilateral stricture and colon bacillus pyelitis. We have dilated the strictures and cleared up her pyelitis by lavage and she still has a nagging trigonitis and is planning to have her bad tonsils removed.

It is of great importance to remember that symptoms due to ureteral stricture often begin in early childhood (see Figs. 24, 25, 26, 30, and 36).

*Urinary Examination and Diagnosis.*—In the section on symptoms we stated that the urine may be quite normal. This has undoubtedly been a source of frequent error in the past. Given a patient with symptoms that suggest trouble in the urinary tract, we have been willing to exclude the urinary tract on finding a normal urine. If the patient's symptoms strongly suggested stone in the ureter we have had X-rays taken. We have the word of the X-ray experts that they miss anywhere from 15 to 30 per cent of ureteral stones—a fact that alone should call for an examination with the wax-tipped catheter in all cases of suspected stone. With the facts that the unassisted X-ray will miss all ureteral stricture cases and that the urine may be normal, we have thrust upon us a duty heretofore neglected, namely, to have all questionable cases investigated with specially prepared catheters and perhaps with the thorium X-ray.

In the second group of 50 cases there were 39 without infection of the urine. We have definite notes on the examination of the urine catheterized from the bladder in 36 of these non-infected cases, and it was normal in 26 cases, contained red blood cells in 5 cases, leukocytes in 2 cases, and both red and white cells in 3 cases.

*Palpation.*—There is often tenderness in the renal region and the kidney may be somewhat enlarged and very tender during one of the acute attacks of pain. The usual phenomena of an intermittent hydronephrosis may be demonstrated if this condition be present.

Palpation of the ureter over the pelvic brim may elicit tenderness and a desire to void. This tenderness over the region of the pelvic brim has led to many useless appendix operations. With both conditions in mind when palpating, one can usually differentiate between them, as the patient will indicate that her usual area of pain is deep in the pelvis, back of the symphysis, although one may elicit more tenderness over the pelvic brim on abdominal palpation and mistake it for an indication of appendicitis.

Vaginal palpation will show the maximal tenderness to be in the broad ligament region in a vast majority of cases, and one may actually palpate the node of thickening which in some cases cannot be differentiated from stone in the ureter.

One may easily mistake the ureteral tenderness for a painful ovary. In Case 56 the patient, then aged 40 years, consulted me first 5 years ago complaining of some of the disturbances of the menopause and a nagging pain low in the left pelvis. She had been advised to have a left oöphorectomy. I found that the left ovary, while apparently extremely tender, was of less than normal size, feeling like a senile fibrous ovary. I advised against operation. She recently consulted me again, having suffered intermittently with the same pain



and finding it recently much exaggerated after a long automobile ride. She had also developed marked pain in the left kidney region and feared that she might be developing cancer.

I suspected ureteral stricture and found on bimanual examination, just as I had noted 5 years previously, that the left ovary was small and hard and apparently very sensitive. By carrying the ovary medianward and isolating it from the broad ligament region I found that it was not at all tender. Then by dropping the ovary and palpating the ureter by itself, I found the latter to be the seat of pain and tenderness. Two dilatations of her left ureteral stricture have resulted in a most satisfactory clearing up of symptoms of 6 years' duration. There was a draining abscess at the root of one tooth and she was referred to her dentist to have X-rays and the necessary dental work attended to.

*Cystoscopy* is usually quite negative, but in the occasional case in which the stricture is near the bladder wall there may be redness and edema about the ureteral orifice suggesting the picture seen with a low ureteral stone. One of the most suggestive points in cystoscopy is the finding of a urethral stricture when preparing the urethra for the cystoscope. Although stricture of the female urethra is common after a gonorrheal infection I have learned by experience to give its presence considerable weight in the diagnosis of a suspected ureteral stricture. We have neglected to make any note on the condition of the urethra in many cases, but in the last 50 cases a note was made in 28, and in 27 of these there was a stricture of the urethra. I think complete notes would have shown at least 60 per cent with a urethral stricture. It is curious that definite annular stricture of the urethra may be present in some cases without bladder symptoms and with a perfectly healthy looking urethral mucosa.

*Catheter Test.*—The crucial test in diagnosing ureteral stricture is made with the wax-bulbed catheter. This, with other instruments used in getting past and treating stricture, will be described under the section on treatment. I do not consider obstruction to an entering catheter as diagnostic of ureteral stricture. Repeated obstruction at the same point is certainly suggestive, but for a positive diagnosis I depend entirely upon the obstruction or "hang" of the wax-bulb on withdrawal. Obstruction of the tip at a certain point in the ureter and then obstruction of the entering bulb at the same point, and the going by of the bulb with a jump and a sense of scar-tissue grating, are points upon which the experienced cystoscopist may rely with a fair degree of safety; but there are many conditions which may obstruct a catheter on entering, and it is better to depend upon the "hang" of the bulb, its jump, and scar-tissue grating sensation as it comes through the stricture area on withdrawal. In the case illustrated by Figures 8 and 9, I did not get by the obstruction until the third attempt at intervals of 10 days, and then only by changing the position of the patient from the knee-chest to the right lateral position while using a considerable amount of force on the catheter with the stylet in. I considered this a stricture case because of the great difficulty in getting by, but after getting the thorium X-ray and before

development of the plates, I said the case was not one of stricture because on withdrawal of the bulb there was only the faintest obstruction at the pelvic brim region, just as one can detect as the bulb comes through the bladder wall and again as it comes through the sphincter urethræ. It has been a source of great satisfaction to my associates in this work and to myself to find at operation in a number of cases how accurately the wax-bulb has located the position and the number of strictures; and how, in other cases like the one just cited with ureteral obstruction but no "hang" of the bulb on withdrawal, the operation has explained the cause of the obstruction.

Dr. Holmes, resident gynecologist at The Johns Hopkins Hospital, asked me to test a ureter in which he had found great obstruction to the wax-tip and wax-bulb catheter on entering, but no appreciable obstruction on withdrawal of the bulb.

Mrs. H., aged 43 years, had been operated upon some several years previously, the right ovary being removed. She complained of a constant pain in the lower right quadrant and at times when this got worse she also had pain in the right back and across the abdomen. I found, as Dr. Holmes had done, that it was very difficult to pass a renal catheter through the pelvic portion of the ureter, but that the wax-bulb returned without appreciable obstruction. The passage of the catheter caused a pain like her former pelvic pain, and injection of the kidney pelvis induced her old pain in the right back. At operation we found that the patient had a much infiltrated and adherent appendix. The former ovarian operation had been followed by a dense adhesion of the sigmoid to the region of the right ovarian vessels. The pelvic peritoneum was reddened and thickened and on opening this and exposing the right ureter, I found that it had left the peritoneum and was adherent to the outer pelvic wall as a result of a marked periureteritis. With a tape under it the ureter was lifted and explored to its entrance into the bladder without the discovery of any local infiltration. It is probable that the hooked-up sigmoid or the appendix, or both, caused a chronic pelvic peritonitis, and when the pelvic inflammation grew worse, there was enough swelling of the ureteral tissues to cause partial stasis and her pain in the kidney region.

In a recent case in which there was much discussion as to the diagnosis, operation revealed a ureteral stricture where our wax-bulb had located it, at a point beneath the uterine vessels, or 8 cm. from the external urethral orifice.

Mrs. W. was referred to me in March, 1917, by Dr. Harry Adler, with a probable diagnosis of gall-stones and appendicitis. Roentgenography had shown small shadows in the gall-bladder region and a bismuth stasis in the ileocecal region after 24 hours. Because of their multiplicity and lack of special characteristics in her symptoms I decided to test for ureteral stricture. This was definitely located in the broad ligament and some of her former symptoms were duplicated by injection of the kidney and manipulation of the stricture. On the day of operation and after the patient was anesthetized, I passed a No. 8 renal catheter prepared with a large wax-bulb, and left this in place during the operation.

Because of a wide diastasis of the rectus muscles a long mid-line incision was made. A definitely diseased appendix was removed, and ileocecal bands and sigmoid adhesions were freed. Gall-stones were palpated and before making the separate gall-bladder incision I investigated the ureter. With its contained catheter it was easy to palpate the ring of thickening in the broad ligament region. The posterior peritoneum was opened to expose the ureter and an assistant then removed the catheter. It slid out

easily until the bulb caught in the stricture area, when the tug displaced and straightened the lower half of the pelvic ureter. After the catheter was out my assistant easily palpated the stricture area.

It is important to remember that one may pass the ordinary renal catheter of large size without detecting a stricture. The presence of a hydronephrosis should make one suspect stricture and test for it with the wax-bulb. In the case of a pyelitis in which catheterization is followed by fever or a chill, one should suspect stricture and should wait at least a week before making the next test with the wax-bulb. Some cases without infection show a marked reaction after catheterization, having an elevation of temperature and an unusual amount of pain and sometimes nausea and vomiting. Any of these unusual reactions after the passage of the ordinary catheter should prompt one to test for stricture. In some of my pyelitis cases I have not suspected stricture until the patient failed to show improvement after repeated lavage. Figure 6 shows a case in which I had washed with silver nitrate solution 6 times and then only had suspected stricture because of the lack of improvement in the pyelitis.

In Case 49 (Fig. 24) I diagnosed stricture from the correspondence about the case, this indicating that the patient had but one kidney and that this was the seat of an infected hydronephrosis. She was getting lavage treatment but frequently had high fever, chills and prostration after the treatment. My correspondent also informed me that she had lost one kidney by operation at the age of 22, after suffering with intermittent hydronephrosis attacks since babyhood, and that she had always been subject to tonsillitis.

*Roentgenography.*—The taking of pyeloureterograms is not necessary in making a diagnosis except in the few cases in which we cannot go by an obstruction in the ureter. Under such conditions if we can pass an X-ray catheter with a whistle tip to the point of obstruction, we can often get the contrast solution to go beyond the obstruction and intensify a stone, if it be present, or outline the character of the obstruction and the condition of the tract above.

In Case 50 (Fig. 15) we failed on several occasions to get enough thorium past the stricture to get a shadow in the kidney pelvis. Urine with pus and blood was coming from the kidney.

In a recent case (Fig. 23) we were arrested at an obstruction on two occasions and then had the nature of the case cleared up by injecting thorium beyond the stricture into the ectopic kidney. Later we successfully dilated the stricture and gave the patient relief from symptoms of 15 years' duration.

Although the X-ray is not necessary in making a diagnosis in most cases of ureteral stricture and although I refused to use it in my early cases when we were dependent on collargol with its dangers, I now use it in most cases for the satisfaction of its confirmatory value and because I find that thorium may be used with impunity if employed with judgment.

Figure 27 is from Case 16. The patient died in uremia without passing urine for 12 days after this thorium picture was taken. I attribute the death not to the use of thorium but to the treatment of both sides at the same time, that caused

swelling and closure of both ureters. During the lavage of her kidneys one at a time at intervals over the previous 4 years she occasionally had a severe reaction—fever, chills, nausea, vomiting, headache, and prostration—and this should have been a warning not to traumatize both sides at one time.

For work on the male subject with the unavoidable restriction in the use of instruments, the pyelogram will prove one of the best aids in diagnosis of ureteral stricture.

The ureterogram is of great value in deciding whether a small shadow on the unaided X-ray plate is within the ureter or whether we are dealing with a phlebolith. This point can usually be easily settled in women by using the wax-tipped and wax-ringed catheter. In using the radiogram method the opaque catheter or the styletted catheter should be photographed in the ureter. Many stones in the ureter are in the broad ligament region, and this is true for many phleboliths. Hence, it is safer to use the bifocal method, as a phlebolith in the uterine vein may be superimposed on the renal catheter and with a flat plate we cannot make a certain interpretation.

Of even greater value is the use of these methods to differentiate ureteral stricture from supposed stone in the ureter when the unaided X-ray has shown a shadow in the ureteral region. Many surgeons have had the uncomfortable experience of operating on at least one of these cases. The patient complains of symptoms suggesting stone in the ureter, the urinary examination confirms this view, and the X-ray shows a shadow in the ureteral region.

Figure 28 illustrates a case of pyelitis occurring 4 months after the birth of a first child, and in which full investigation changed the diagnosis from a right pyelitis due to stones in the ureter to bilateral stricture with right pyelitis. Figure 29 illustrates a case referred by Dr. Hugh Trout of Roanoke, in which I was fortunate enough to get by her dense stricture with the X-ray catheter and demonstrate the extra-ureteral position of the stones. Figure 30 represents an X-ray plate brought with a patient referred by Dr. E. L. Mortimer, as a case of left pyelitis due to stone in the ureter. Investigation failed to show scratch marks and demonstrated that her bilateral pyelitis following childbirth was due to stricture. Figure 31 illustrates the case of a patient with a stone in the appendix and gall-stones, the symptoms being due to ureteral stricture.

*Diagnosis from Tuberculosis.*—Great care must be exercised not to mistake tuberculous disease of the ureter for ordinary stricture. In 1901, I did a resection of the ureter and implantation into the bladder on a patient who had much pus in the urine, and an impassable thickening in the lower end of the right ureter. One examination had shown no tubercle bacilli. The true diagnosis was revealed a few months later, when I was called to operate on the patient for intestinal obstruction, which was found to be due to tuberculosis. The tuberculous kidney was removed later and the patient made a good recovery.

In October, 1915, Dr. Charles Austrian referred to me a young unmarried woman, 22 years of age, who had been having a great deal of pain in the left pelvis and left kidney region, and bladder symptoms for about two years. She had had ton-

sillitis since childhood. She had had two operations, a dilatation and curettage, and a suspension of the uterus and appendectomy. After one successful dilatation of an obstruction low in the left ureter and the demonstration of a pyelitis, I was unable on several occasions to dilate again. I was planning to expose the ureter extraperitoneally and do a retrograde dilatation, when at a final cystoscopy I was impressed with the large amount of edema about the ureteral orifice and made a second search for tubercle bacilli, which resulted in demonstrating them in large numbers. Nephrectomy for tuberculosis resulted in a restoration to health.

Figure 32 illustrates a case in which I had successfully relieved the uncomfortable symptoms by dilating the stricture and in which I first suspected tuberculosis because the patient's large amount of pus failed to diminish after repeated lavage. My suspicions were increased when on getting this pyeloureterogram we saw the irregularly eroded character of the pelvic outline. A search for tubercle bacilli was positive.

*Differential Diagnosis.*—It may be well to close this section on diagnosis by giving a list of various diagnoses made upon these patients although their symptoms were chiefly due to ureteral stricture. *Urinary tract:* cystitis, pyelitis, pyelitis of pregnancy and the puerperium, pyonephrosis, floating kidney, hydronephrosis, stone in the ureter, chronic Bright's disease. *Genital tract:* pelvic inflammatory disease, ovarian disease. *Gastro-intestinal tract:* various functional disorders of the stomach and intestines, chronic peritonitis, intestinal adhesions, sigmoid adhesions, colitis, chronic pancreatitis, gallstones, appendicitis. *Joint and nerve conditions:* lumbo-sacral and ilio-sacral joint pains, neuralgia of the sacral plexus, sciatica. Mental disorders.

*Treatment.*—The chief end sought in treatment is the relief of symptoms, and in the infection cases a urine freed from infection, and in all cases suitable for dilatation such a thorough opening of the stricture area that there will be no recurrence.

There are very few cases in which we cannot at least ameliorate the symptoms, and fortunately we can relieve the patients, to a large extent, if not entirely, in the majority of cases. There are very few cases of pyelitis in which we fail to do away with the infection. I believe that time will demonstrate that in many cases we shall not get a permanent dilatation of the stricture, and complete relief of symptoms until we have eradicated the original focus of infection.

The ideal treatment for stricture of the ureter is by dilatation from the vesical approach. Naturally those whose work is confined to women and those who use the Kelly speculum have a great advantage in treating this disease. Various forms of operative cystoscopes and ureteral instruments have been devised by Bransford Lewis and others, which make it quite possible to do much effective work from the vesical end in the male.

My work being confined to women, I shall speak only of the methods which I have used in treating stricture, these having been largely developed or suggested by Dr. Howard A. Kelly.

A glance at Figure 33 will show the simple instruments which I use, entirely with the tubular speculum of Kelly. As a rule I use the olive-tip catheter (Nos. 7, 8, and 9) carrying a wax-bulb 8 to 10 cm. from the wax-tipped end (b). Not infrequently, when the olive-tip catheter refuses to pass, a round-tip (a) or a whistle-tip (c) will engage in the lumen and go by the stricture. One may use the ordinary whistle-tip catheter with the wax-bulb or the whistle-tip catheter with a gradually increasing diameter, which Garceau devised for the special purpose of making functional tests (c). This Garceau catheter (Nos. 11 or 13) gives a fairly good dilatation without the addition of the wax-bulb.

At times these catheters engage in the lumen of the stricture area better with the wire stylet left in for stiffening, and at times a slight withdrawal of the stylet will result in success when the catheter has seemed permanently obstructed.

In case of failure to get by with any of these forms of flexible catheter, it is sometimes possible to make the first entrance with the metal searcher (f). By slightly curving the last centimeter of the metal searcher, one can gently rotate the angled handle, thus giving the tip a variety of axes, in one of which it will engage and pass the stricture where the more flexible instruments will meet a pocket or shelf of mucosa and be permanently obstructed. Usually after getting through the stricture area with the olive-pointed metal searcher, one can withdraw the searcher and immediately get by with one of the flexible catheters which has previously been held; or one can follow the metal searcher with the metal bulb dilator (g), which has a slightly curved olive-tip, followed by a metal bulb. 3 mm. in diameter, which gives such thorough dilatation that the flexible catheter is quite certain to pass. At later treatments, where a still greater dilatation is desired, the metal bulb dilator 5 mm. in diameter (h) may be used. It is seldom necessary to use this large metal bulb, for one can easily use the flexible catheters with a wax-bulb as large as 6 mm. in diameter. In using these very large bulbs it is well to see that the bulb is of a perfectly spindle shape, having no abrupt shoulder to catch on the stricture.

In our earlier work in testing for stone in the ureter we always used beeswax (the *cera flava* or *cera alba* of the pharmacopœia) mixed with one-third or one-half of sweet oil, but I found that this softens the wax to such a degree that it is partially crushed on coming to a narrow orifice, or later on meeting the stricture; sometimes on withdrawal of the catheter, a part or all of the wax is left on the proximal side of the stricture. For these reasons I have given up the mixed wax and oil and use only the pure beeswax. This is soft enough to get a good impression from a stone, and it is firm enough to hang to the catheter and not be crushed under any ordinary condition of obstruction.

At times on failing to get any of the above instruments to engage in a stricture, I have succeeded in making the first dilatation by using the whalebone filiform searchers (e). Usually the first two or three searchers catch in the mucosa just as the other instruments have done, but after introducing three, four, or five filiforms, one can by careful manipulation get one



of them through the stricture lumen, and then on further manipulation the others can be made to follow.

After dilatation with from two to four filiforms, one can withdraw these and pass the renal catheter with the bulb, but it is generally safer to leave one or two of the filiforms as a guide and pass the metal searcher or the flexible catheter alongside the filiforms to engage the stricture lumen before the guides are withdrawn.

Before beginning work with the whalebone filiforms one should have sterile hands or put on a sterile glove, for these have to be grasped close to the speculum at a portion of the filiform that later enters the bladder or the ureter.

Finding by experience that the whistle-tip catheter often engaged and passed a stricture after the pointed tip had failed, and finding that the metal searcher with a slightly curved tip was a most useful instrument, apparently because a rotary motion enabled the curved tip to pick up different axes of direction in the lumen, I combined these two ideas of a beveled tip, and a fulcrum to throw the tip into various axes, by using the wax on the end of an ordinary pointed-end catheter, in a fashion to make a corkscrew or spiral-tip catheter (see Fig. 34). I have been successful in passing strictures with this spiral tip after failing with all other instruments. One can feel the rotation of the catheter as the spiral tip finds its way through the stricture.

*Precautions in Technique.*—Experience has taught a few precautions which should be observed in treating stricture. If the history points to the probability of bilateral stricture, never investigate both sides at the first examination, and in later treatments do not dilate both sides at one sitting until you are certain that the strictures are well dilated and that the kidneys will have drainage after the trauma of treatment. Case 16 (Fig. 27) emphasizes these points.

Do not investigate or treat a stricture too frequently. It seems to take about 10 days in the average case for the traumatic edema of the early investigation to subside. This is particularly true if the last effort to dilate was a failure, for in such a case there is usually more trauma than in the case in which the catheter and dilator pass on the first effort. If the patient is away from home and under the expense of hospital treatment she may be restive at the surgeon's apparent inactivity, and it is well to explain that greater haste is likely to defeat the desired end. For the patients who return to my office or to the dispensary for treatment I prefer to fix the interval at from 2 to 4 weeks or longer, according to the response.

In the pyelitis cases in which we are anxious to combine the pelvic lavage, we may observe the 10-day interval for the first two or three treatments or until we are quite certain of a good dilatation, then we may use lavage twice a week, employing a small catheter (No. 5 or 6) and once in 10 days or 2 weeks using a No. 8 or 9 catheter with the large wax-bulb for dilatation.

In any case do not use a large bulb for the first dilatation. A 3 or 3.5 mm. bulb will usually pass without splitting the mouth of the ureter and without too much trauma to the stricture area, although this small bulb may split the stricture and

cause some bleeding. It is not uncommon in the pyelitis cases to have a partial closure of the stricture area after the first one or two dilatations with the small bulb; this being especially true if these treatments are at short intervals.

The use of large bulbs measuring 5 to 6 mm. is not without its danger even after the patient has had repeated treatments. In Case 35, the patient who had only one kidney (see Fig. 35) was ready to be dismissed as well when we undertook to make a final large dilatation. This evidently split her stricture area for she had intermittent suppression and passage of ureteral clots, and was in a precarious condition for several days until the bleeding stopped.

In two of my cases the use of too large a bulb or perhaps the presence of a too abrupt return shoulder on the wax-bulb resulted in great difficulty in extricating the catheter, and on its return the shoulder carried a complete collar of mucous membrane torn from the stricture area. This of course represents an undesirable degree of trauma in the stricture area.

One must use care in the amount of force exerted in pushing the catheter in. If the stylet is still entirely in the catheter the end of the catheter may go through the ureter. This evidently happened in Case 36, and a silver nitrate injection of 1:1000 strength was left in the extraperitoneal tissues of the pelvic brim region. This caused much pain of a peritonitic character which persisted for nearly a week but with no apparent permanent damage. In Case 29 the catheter went through the bladder portion of the ureter, penetrated the bladder mucosa, and curved back into the bladder.

If the stylet has been partially withdrawn there is probably no danger of the end of the catheter penetrating the ureter, but forcible pushing may result in penetration of the catheter wall with the end of the stylet and probable puncture of the ureteral wall, as occurred in a recent case without observable results.

*Results of Treatment by Vesical Approach.* What can we hope for in the simpler non-operative forms of treatment? In the cases without infection and without much renal disturbance we can look for cure, if distant foci of infection have been removed. This was the result in 8 of my first 50 cases. The case numbers, the duration of symptoms, and the pelvic contents before and after treatment are shown in the following table:

Case No.	Duration of symptoms	Pelvis before treatment	Pelvis after treatment
15	A few weeks.	30 c. c.	3 years later, 15 c. c.
17	5 years.	22 c. c.	2 years later, 9 c. c.
21	2 months.	16 c. c.	6 months later, 7.5 c. c.
22	5 years before passing ureteral stone.	28 c. c.	5 months later, 10 c. c.
27	2 years.	30 c. c.	Not seen after 3 treatments and complete relief of symptoms.
28	9 years.	15 c. c.	3 years later: No further attacks. Pregnant for 3d time since treatment.
35	18 months.	22 c. c.	4 months later, 10 c. c.
40	3 months.	40 c. c.	Not seen after two treatments.

Since presenting the above table in my preliminary report of the first 50 cases, one patient (Case 15) has returned with renewed symptoms on the left side and similar symptoms on the opposite side. Dense strictures were present on both sides. Another patient (Case 35) soon returned and her kidney pelvis reached a capacity of 32 c. c. After the extraction of abscessed teeth the stricture responded to treatment and when last seen several months ago, she was free from kidney symptoms and the pelvis held 10 c. c.

In certain other cases, even with infection, if the kidney pelvis is not too dilated, we get brilliant results in permanently clearing up the symptoms and the infection through dilatation and lavage. This occurred in 6 of my cases, 2 with bilateral stricture and pyelitis.

Case No.	Duration of symptoms	Pelvis before treatment	Pelvis after treatment
34	11 years.	Bilateral and no dilatation.	Free of pus and bacteria.
41	1 year or less.	30 c.c. Staph. Free of pus and cocci.	Pelvis content 8 c.c. 6 months later.
43	4 months.	Bilateral. Colon. No dilatation.	Free from pus and bacteria.
47	Pyelitis, one week.	11 c.c. Colon.	Free from pus and bacteria.
49	10 months.	40 c.c. Colon.	Free from pus and bacteria. Pelvis content 30 c.c. two months later.
45	Pyelitis 3d month of pregnancy. 4 days' duration of symptoms.	18 c.c. Bacillus.	One dilatation with 5 mm. metal bulb. No further symptoms. Examined one year later, and urine normal.

After presenting the above table in my preliminary report, two patients (Cases 34 and 43) both returned with bilateral colon pyelitis. The first (Case 34) was dismissed as well in January, 1915. She again began to have some frequency and discomfort in August, 1915. In January, 1916, 14 teeth were extracted by Dr. Brun, all having bad areas about the roots. She returned in January, 1917, complaining of bladder symptoms and general malaise as on her first visit. After getting the bladder approximately normal and still finding a good deal of pus in the urine, I investigated both kidneys in April and found bilateral strictures and pyelitis. The right kidney was sterile after 2 treatments with 1:500 silver nitrate solution. The left kidney still showed some infection June 1, but she was practically free from symptoms and her general health had improved markedly.

The other woman (Case 43) was dismissed as well in July, 1915. In January, 1916, she returned during an attack of gripe, fearing that her trouble had returned. Investigation of the kidneys showed negative cultures and the ureters apparently well dilated. In February, 1917, the patient was "run down" and had a "slight cystitis attack." She reported in April, 1917, when bilateral pyelitis was found. The left side cleared after a few treatments, but the right side still shows infection (June 1, 1917).

In other cases with infection and large pelvis we may be unable by lavage to rid the patients of infection, probably

because of the permanently sacculated pelvis, but we may restore them to apparent health by doing away with the obstruction in the ureter, thereby relieving their pain and their toxic symptoms (see Fig. 27).

In the following 2 cases with infection the symptoms were relieved by treatment, but I have been unable to follow the patients with a cystoscopy to learn of the final kidney condition.

In Case 14 there were attacks of pain in the kidney for two years, enlarged inflamed tonsils, and arthritis, a stricture about 3 cm. from the bladder, and a kidney pelvis of 12 c. c. capacity with a staphylococcus infection. After a few dispensary treatments she was lost track of.

In Case 23 there was a stone in the bladder to which all the symptoms were referable. The X-ray picture revealed another small shadow in the left ureteral region. On investigation this shadow was found to be outside the ureter, but the ureter had a stricture in the bladder portion and another about 4 cm. from the bladder. The kidney pelvis held 21 c. c. and was infected with the colon bacillus. After a few treatments the strictures were well dilated and the pelvis reduced to 14 c. c. The patient went to her home in North Carolina before the infection had disappeared, but a recent letter, 4 years after her treatment, states that she is perfectly well.

In another group of 3 cases of bilateral, infected pyelitis, the method has not had a fair trial, because of a failure of the patients to persist with treatments after securing enough dilatation to free them from the severe attacks of pyelitis.

Of my second group of 50 cases many are still being treated. Fifteen have been dismissed as well. Thirty-one are classed improved, some of these being practically well, others but little improved. Three had but 1 preliminary investigation and have not been seen since. One had several painful treatments without apparent improvement and, on being urged to have some bad tonsils removed, she ceased treatments.

*Treatment by Operation.*—When all the methods of vesical approach fail, we have to consider operative measures. No form of operation should be undertaken until as complete investigation as possible has been made of both sides. Stricture of the ureter being bilateral in 30 per cent of the cases, we cannot afford to take anything for granted in dealing with a case in which symptoms may be confined to one side.

If investigation shows stricture of only 1 ureter, associated with a kidney of little or no functional value, conservatism usually calls for extirpation of the injured or dead kidney. This was done in 6 of my first 50 cases with entirely satisfactory results.

If the stricture is high at the junction of the kidney pelvis with the ureter, we may follow Fenger in doing some form of pyelo-ureteroplasty. Actual stricture at this point is extremely rare, and the valve-like obstruction formed by floating kidney can usually be overcome by mere high fixation of the kidney, as I have found in a number of cases.

If careful examination at the time of operation leads one to suspect an organic narrowing at the pyelo-ureteral junction, a pyelotomy and careful dilatation may be done in addition to the kidney fixation, or if the pelvis is very large, a partial



pyelotomy may be done, care being taken to dilate if the orifice into the ureter is at all narrowed.

In Case II with symptoms of 1 year's duration there was a stricture in the left broad ligament region and a kidney content of 360 c. c. of clear urine, the functional test being good and equal on both sides. I resected her kidney pelvis and later examination showed the restored pelvis to hold 750 c. c.

If the stricture is lower and about the lumbar or pelvic brim region, it has been recommended to cut through above the stricture and implant into the colon or in the loin region.

If the stricture is low and near the bladder, as a vast majority of these strictures are, it has been the custom to implant the severed healthy end into the colon or bladder. I have never made a colon implantation in these cases, but the results of Coffey's work on dogs<sup>11</sup> and of Charles Mayo's work on the human, with Coffey's method, would indicate that there is a field for this method. Some of these patients have a degree of dilatation of the ureter, which would make the operation easier than on the normal ureter, and some of them have such a wide dilatation of the ureter that the operation would be more difficult and the lowered resistance of the kidney would invite infection.

I have done a bladder implantation in 2 of the first 100 stricture cases with indifferent or questionable results in both. I say "questionable results" because in neither case could I later enter the ureter with a catheter from below. Both patients have been in good health since the implantation, but I suspect in both of these cases that there may have formed stricture at the site of the implantation with gradual destruction of the kidney.

*Retrograd Dilatation.* I wish to emphasize a method for handling these cases by operation which I have not seen mentioned in the literature but which I am sure must have been employed by some surgeons and which has probably been described before, *viz.*, the treatment by retrograde dilatation. Certainly every surgeon must follow his ureteral stone extractions by dilatation of the usual area of infiltration about the stone.

The ureter is exposed by the extraperitoneal route; incision is made into its dilated portion above the site of stricture, and increasing sizes of the French gum elastic bougies (Fig. 33d) or metal sounds are passed until the stricture is dilated to a diameter of from 5 to 7 mm. The ureteral incision is then closed with catgut. A wick drain is usually left in the extraperitoneal incision for 48 hours to take care of possible contamination by the escaped urine at the time of operation, or of post-operative leakage and the excessive serum secretion following the extraperitoneal operation.

If the dilatation has not been entirely satisfactory or if there has been much trauma to the ureter, I leave it open or close it incompletely with catgut to favor urine drainage in case of temporary swelling sufficient to close the traumatized stricture area. In such cases 2 or 3 small wicks are dropped

to a point near the ureteral incision and left for some days or until there is certainly no urine leakage.

A McBurney incision is suitable for most of these cases, but a semilunar line incision is more useful, for it can be enlarged up or down to suit the exigencies of the case, and through a moderately long semilunar line incision one can easily palpate from kidney pelvis to bladder.

With care one can preserve the intercostal vessels and nerves crossing this incision to the rectus muscle simply by deflecting them and working between them.

I have treated 9 of the first 100 cases by this retrograde dilatation, 6 cases in which it was impossible to dilate from below, 2 cases in which stricture of the ureter was found when stone was being looked for, and 1 case in which ureter stricture had been successfully treated from the vesical approach one year previously, but the stricture again swelled shut sufficiently to cause kidney symptoms in the course of an attack of acute gonorrheal salpingitis.

The results in these 9 cases treated by retrograde dilatation have been perfect in 7, so far as measured by relief of symptoms and ability to easily catheterize later from below. In one case, my first one in which I was looking for stone and failed to find it but found the ureter dilated to a diameter of 1 cm. from the bladder to the dilated kidney pelvis, I found a dense stricture in the bladder area and dilated it with the uterine sound only, which probably made a diameter of only 3 mm. I heard one or two years later that this patient developed symptoms again and had a stone removed from the kidney. I have questioned the accuracy of this report, especially as the patient had the kidney removed at a third operation. It is possible that I overlooked a floating stone temporarily lodged in a kidney calyx, but I think it more likely that the symptoms returned and persisted because the stricture was not sufficiently opened. My X-ray picture had shown a questionable shadow in the kidney region.

My second case with a questionable result after retrograde dilatation was one in which the stricture of the left ureter was a diffuse one, reaching from the bladder to 5 or 6 cm. above. The woman had a stricture of the right ureter also, but no symptoms pointing to this side. A few weeks after retrograde dilatation she again showed signs of kidney obstruction and I failed to catheterize from below. I attempted to make a uretero-vesical implantation above the site of the stricture, but failed to find the ureter in the midst of the scar tissue following the previous operation.

The patient got along fairly well and when she was 3 months pregnant, some 3 or 4 years later, her physician at my suggestion tried to catheterize her ureters, but was unable to enter either kidney. One would suppose that with the increased circulation and pliability of the tissues characteristic of the pregnant state, this would be an ideal opportunity for dilating strictures of particular density.

The cases least suited for retrograde dilatation are those in which previous testing of the capacity of the kidney pelvis and ureter and pyelography have shown an absence of marked

<sup>11</sup> Jour. Amer. Med. Assn., 1911, Feb. 11, 397.

enlargement of the lumen above the site of stricture. In these cases the ureter is found to be too small above the stricture to admit large dilators, and if it is at all possible to get by from the vesical approach, one should be satisfied to do as well as possible by this route although it may require a long, tedious course of treatment.

I cannot speak with authority concerning ureteral stricture work in the male. Because of the restriction in the use of instruments, it is probable that retrograde dilatation will be resorted to much more frequently in the male than in the female. Dr. Bransford Lewis has devised a clever flexible

metal dilator which will undoubtedly be of use in some cases. In many cases this instrument will be found to be too blunt to get by the stricture area. Those who use male instruments that take a No. 8 or No. 9 renal catheter will be able to relieve many cases merely by passing the catheter, particularly if the dilatation can be repeated every few weeks or months. In the past, many patients suffering from hydronephrosis and from pyelitis due to stricture have been improved or cured of their symptoms without discovery of the stricture because the passage of a renal catheter gives sufficient dilatation in some cases to result in good drainage.

## THE CHIEF FUNCTION OF THE OBLIQUE MUSCLES OF THE EYE SOME OBSERVATIONS WHICH SEEM TO LEND SUPPORT TO A LONG DISCARDED THEORY

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In endeavoring to find an answer to the question, What is the chief function of the oblique muscles of the eye?, it is important that we should take into account the fact that these muscles are not peculiar to man, but that, on the contrary, they are found, almost without exception, in all vertebrates—the only exception being the myxinoidea or lampreys. This fact, which shows that they were evolved many thousands of years before even the anthropoids made their appearance, seems to indicate that they have a much more important function to serve than that which is commonly attributed to them in man—that their chief office is to counteract the faulty action of the superior and inferior rectus muscles, owing to the fact that the direction of the pull of these muscles does not correspond with the sagittal axis of the eyeball. Surely these conditions do not exist generally in vertebrates, and, therefore, could have had no bearing on the evolution of the oblique muscles.

In the early part of the last century, the commonly accepted view, which, according to Prof. Joseph Pancoast, dates back to the time of Boerhaave, was that the oblique muscles were the antagonists of the recti and, especially, that they prevented the latter, when acting, from retracting the eyeball into the orbit. This view, however, was not without its opponent, and the first instance I have found of its rejection occurs in an article by Green,<sup>1</sup> in which the author says:

To the favorite doctrine of most anatomical writers, we cannot subscribe, viz., that the obliqui are the antagonists of the recti. This error is based on another, viz., that there is a necessity for antagonism, i. e., that the recti retract the ball from its ordinary position in the socket.

It is to be regretted that, at least in the published abstract of his paper, the writer adduces no facts or observations to sustain these very positive assertions.

<sup>1</sup> Green, C.: On the Functions of the Oblique Muscles of the Eye. Abstr. Boston Med. and Surg. Jour., 1845, xxxii, 191.

Coming down, now, to a more recent time, we find that so careful an observer as Fuchs held that some provision is necessary to prevent the eyeball, when performing its movements, from leaving its place in the orbit, and, according to his view, it is the bulbo-orbital fascia which provides against this misadventure.<sup>2</sup> He says:

By means of this system of fasciæ pervading the orbit, the contents of the latter are fixed in place. It is owing to them that the eye does not leave its place when performing its movements, but turns about a fixed center.<sup>3</sup>

This view of the action of the bulbo-orbital fascia, I may add, is held, also, by Duane,<sup>4</sup> another high authority on the ocular muscles and movements, who recently said:

The position of the eye in the orbit seems to me to be governed mainly by the fascial bands (including the check ligaments) that connect the eye and muscles with the orbital walls.

It requires no little temerity on my part to call in question the competence of the bulbo-orbital fascia to do what these authorities agree in holding it does do—to prevent the eye from leaving its place in the orbit, when the recti muscles contract, and to cause it to turn about a fixed point.

<sup>2</sup> Motais, discussing the fixity of the eyeball in the orbit, in his treatise on the "Anatomie de l'appareil moteur de l'œil de l'homme et des vertébrés" (1887, pp. 123-124), answers the question, How can an organ with such yielding walls, immersed in a soft mass, and subject to such rapid movements, maintain a fixed position?, by saying that it is due to the combined action of several anatomic elements, which he mentions in this order: the antagonism of the rectus and oblique muscles, the bulbo-orbital fascia, with its ligamentous wings, and the cushion of adipose tissue which occupies the deeper portion of the orbit.

<sup>3</sup> Fuchs: Text-Book of Ophthalmology, fourth American edition, p. 689.

<sup>4</sup> Personal communication to the author.

To effect this end, it would seem there must be tense, inelastic bands of fascia connecting the sclera or Tenon's capsule with points on the orbital walls anterior to their attachments to the eyeball. That these bands must be, as I have described them, *tense* and *inelastic*, appears obvious; otherwise, having no power of contraction, they could not effectually oppose the very real backward pull of the several recti muscles.

Do such fascial bands exist? And, if they did, would they not, acting as check ligaments, necessarily interfere with the movements of the eye?

These questions, it seems to me, admit of but one answer: No such bands do exist, and, if they did, the rotational movements of the eyeball would certainly be seriously curtailed.

Accepting the view of Fuchs, which I understand that Duane endorses, that *some* provision is necessary to prevent the eye being pulled back into the orbit by contraction of the rectus muscles, and thus enabled to rotate about a fixed point, it would appear that we must fall back on the discarded theory of the supporting or antagonistic action of the oblique muscles for a solution of the problem.

If this view is correct, it would seem to follow that the oblique muscles must take part in all movements of the eye.



Subjective light sensations seen in left half of visual field by right eye: *a*, produced by lateral rotation of the eye; *b*, by downward rotation; *c*, by upward rotation. The upper light sensation, in each instance, is caused by contraction of the inferior oblique, and the lower by contraction of the superior oblique.

Observations which I have recently made of certain subjective light sensations, manifestly caused by contraction of these muscles, appear to show that such, indeed, is the case, with the possible exception of the conjoint action of the interni in effecting convergence. On awakening in the early morning, while the room is still dark, I have observed, projected somewhat into the upper visual field of each eye and in juxtaposition, always one above the other, two subjective light sensations, one decidedly sharper than the other, on rotating the eyes widely in any direction. On converging the eyes strongly, which I found not so easy to do in the dark, I have thought I obtained similar light sensations, but they were less well defined and more evanescent than those produced by rotating the eyes vertically or laterally.

When the eyes are turned upward, in which movement the inferior oblique should act more energetically than the superior, the brighter and better defined light sensation, as we should expect, is, as shown in the illustration, above, the less defined one, produced by the feebler action of the superior oblique, below. When the eyes are turned downward, the superior oblique being then called into more energetic action, the brighter sensation is below, the feebler one above. When the eyes are rotated laterally, the upper and lower light sensations do not differ appreciably in intensity or in form, indicating,

it would seem, that in these movements the obliques act with approximately equal energy; and the same is true of those which, I believe, I observed on converging the eyes. The phosphenes seen in the left half of the visual field are, of course, projected from the right eye, and vice versa.

I may add that the light sensations described rapidly decline in brilliance, and, with the exception of those caused by rotating the eyes upward, are best observed with the lids closed, and, further, that repeated attempts to produce them, by energetically rotating the eyes, presently give rise to an ill-defined aching sensation, most noticeable, perhaps, in the region of the trochlea of the superior oblique.

If further observation should show that these subjective sensations do not occur in convergence of the eyes for a near point, a possible explanation might be that in regarding near objects a certain amount of displacement of the eyes backward and inward, in addition to their inward rotation, may not be harmful, may, indeed, even be helpful, so that conjoint action on the part of the obliques under such circumstances would not be called for.

As to the competence of the oblique muscles to counteract the backward pull of the recti, and to maintain the eyeball in its proper position in the orbit, it would seem that they are fully equal to the task. With their fixed attachments close to the orbital border—that of the inferior oblique actually and that of the superior oblique potentially, because of its trochlea—and passing from these points to grasp the eyeball near its posterior pole, one from above, the other from below, and, moreover, unlike the bulbo-orbital fascia, having the power to contract, so as to oppose with exactness the backward pull of the recti, the oblique muscles appear to be entirely capable of causing the eye to rotate, with precision, about a fixed center, a provision so essential to accurate vision, and, especially, to perfect binocular vision.

If it be objected that to do this the direction of the pull of these muscles would have to be straight forward, it may be pointed out that the pull of the recti, especially the superior and inferior recti, is not straight backward, and that the direction in which the energy of the obliques is exerted seems really to be that best adapted to accomplish the end in view.

That the oblique muscles serve other important ends, especially in preventing the superior and inferior recti from tilting the vertical axis of the eye, and in assisting those muscles to rotate the eyeball upward and downward, is, of course, not to be denied; but that their *chief* function is that which I have set forth seems, to me at least, to admit of but little doubt.

## NEW PUBLICATIONS.

The following monograph is for sale by The Johns Hopkins Press, Baltimore, Md.:

**Relation of Tonsillar and Nasopharyngeal Infections to General and Systemic Disorders.** By S. J. CROWE, S. SUTTON WALKINS and ALMA S. ROTHBOLT. 63 pages. Price, \$1.25.



## CLINICAL OBSERVATIONS ON THE HEMOGLOBIN AFTER OPERATION

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There are but few observations in the literature on the hemoglobin of surgical patients after operation. Grünwald in 1889 published a series of 10 cases, from which he concluded that there is little or no oligochromemia immediately post-operative, even after abundant hemorrhage. His work, however, does not show when or for how long the hemoglobin decreases. The lowest point of the hemoglobin curve is of interest to surgeons as a clinical estimate of the amount of blood lost at operation. We have been unable to find any data on this point in the literature. According to Laker (quoted by Grünwald) immediately after operation there is no change, or very slight change, in the hemoglobin, but after several days in cases in which there has been severe hemorrhage there is also a great reduction of hemoglobin. After hemorrhage the total blood volume is decreased, the quality of the blood being first changed when it becomes thinned owing to absorption of fluids from the intestinal tract (Hoppe-Seyler and Penzoldt, quoted by Grünwald).

Young says that the hemoglobin immediately after hemorrhage shows no especial change, but that after 6 to 12 hours the percentage is lowered, the fluid content of the blood seemingly adjusting itself temporarily within the first 24 hours.

Boothby and Berry have shown that the percentage of hemoglobin and the red blood cells are increased under conditions of work, causing an appreciable amount of perspiration, and that there is no increase without sweating.

In all probability the most important factors determining the hemoglobin curve, except the loss of blood at operation, are the intake of fluids, at or after operation, by infusions or through the mouth or rectum, and the output in sweat, vomitus, urine and feces.

In the series of cases here reported, we have endeavored to show the effect upon the hemoglobin of operations during which there has been slight, moderate or severe hemorrhage.

## TECHNIQUE

The Sahli Hemoglobinometer was used for hemoglobin determinations, as it is an instrument particularly adapted to general clinical use.

A uniform technique was observed throughout, and in almost all cases one instrument was used for all the readings on a given case. When two instruments were used on the same case, they were carefully checked against each other and corrections made, when necessary. The series of readings on a given case were made by one observer, or, when two took part in it, their findings were carefully controlled and corrections were made when necessary.

In most cases the exact time of an observation has been noted so that the number of hours between any two readings can be determined easily from the tables.

The blood was obtained from the finger or ear, the same source being always employed for any given patient.

In the accompanying tables the date, time and character of the operation are recorded. The loss of blood at operation is only approximately estimated. We lack quantitative data on the intake and output of fluids during the entire time that the patients have been under observation, but notes have been made of all infusions, liquids given by the rectum and of vomiting after operation. Unless otherwise noted, the patients ran the usual course, being encouraged to take water by the mouth as soon as possible.

All of the gynecological patients were operated upon under anesthesia—nitrous oxid and oxygen, followed by ether administered by the open drop method.

## CONCLUSIONS

The hemoglobin readings shortly after operation show very little change when compared with readings made before operation, even in cases of severe hemorrhage. The immediate post-operative reading often shows some increase over the pre-operative reading.

The lowest point of the hemoglobin curve is found usually from 30 to 60 hours after operation (a difference of less than 5 per cent is not considered).

The greatest drop in hemoglobin is usually during the first 24 to 36 hours, and is most rapid when salt solution infusions have been given.

In the series showing only a slight loss of blood at operation, the hemoglobin readings are usually higher during the first 12 hours than those made before operation, and there is very little post-operative decrease at any time.

We wish to thank Dr. Howard A. Kelly for permission to publish these observations.

## LITERATURE

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TABLE I.—HEMOGLOBIN IN CASES WITH VERY SLIGHT BLOOD LOSS AT OPERATION

Gyn. No.	Female	Race	Age	Character of Operation	Operation Date	Blood Loss at Operation	Hb. and blood counts before Operation	After Operation, Day of Operation	2d Day	Day	4th Day
21836	"	White.	24	Dilatation and curettage.	2/5/16. 9.05 a. m.	Very Slight.	2/4/16. Hb. 105%. W. B. C. 10,600.	7.15 p. m. Hb. 107%.	7.15 p. m. Hb. 102%.	7.15 p. m. Hb. 108%.	7.30 p. m. Hb. 105%.
21845	"	"	60	Amputation of cervix. Vag. fixation of uterus. Ant. and post. colporrhaphy.	2/24/16. 10.00 a. m.	Slight.	1/22/16. Hb. 87%. W. B. C. 7,400.	9.45 p. m. Hb. 86%.	9.00 p. m. Hb. 86%.	9.15 p. m. Hb. 85%.	9.15 p. m. Hb. 90%.
21861	"	Black.	28	Ether exam.	2/17/16. a. m.	None.	2/16/16. Hb. 78%. W. B. C. 7,000.	3.30 p. m. Hb. 84%. 7.45 p. m. Hb. 75%.	7.30 p. m. Hb. 72%.	.....	.....
21877	"	"	31	Hysteromyectomy. Double S. O. Appendectomy.	2/9/16. 11.00 a. m.	Slight.	2/8/16. Hb. 80%. W. B. C. 7,600.	6.45 p. m. Hb. 95%.	8.30 p. m. Hb. 96%.	7.45 p. m. Hb. 80%.	7.45 p. m. Hb. 80%.
21878	"	"	42	Appendectomy.	2/8/16. a. m.	Slight.	2/7/16. Hb. 83%. W. B. C. 15,600.	8.00 p. m. Hb. 85%.	6.45 p. m. Hb. 83%.	8.15 p. m. Hb. 85%.	7.40 p. m. Hb. 83%.
21888	"	White.	25	Suspension of uterus. Appendectomy. D. and C. R. R. V. O.	2/10/16. 9.30 a. m.	Slight.	2/9/16. Hb. 95%. W. B. C. 5,440.	8.00 p. m. Hb. 101%.	7.30 p. m. Hb. 103%.	7.30 p. m. Hb. 99%.	7.30 p. m. Hb. 93%.
21891	"	"	16	D. and C.	2/29/16. 8.20 a. m.	Very Slight.	2/18/16. Hb. 90%.	1.00 p. m. Hb. 101%. 7.45 p. m. Hb. 95%.	8.00 p. m. Hb. 100%.	7.15 p. m. Hb. 90%.	7.45 p. m. Hb. 93%.
21913	"	Black.	38	Hysteromyectomy. Appendectomy.	2/23/16. 9.45 a. m.	Slight.	2/22/16. Hb. 40%. W. B. C. 11,600. 2/23/16. 9.00 a. m. Hb. 38%.	11.00 a. m. Hb. 34%. 9.00 p. m. Hb. 44%.	7.15 p. m. Hb. 48%.	8.00 p. m. Hb. 41%.	7.45 p. m. Hb. 43%.
21914	"	"	41	Hysteromyectomy. Double S. O. Appendectomy.	2/14/16. 9.30 a. m.	Slight.	2/8/16. Hb. 53%. W. B. C. 5,400.	12.00 Noon Hb. 67%. 7.15 p. m. Hb. 68%.	.....	7.30 p. m. Hb. 55%.	8.00 p. m. Hb. 50%.
21933	"	White.	34	Hysterectomy. Double S. O.	2/8/16. 10.45 a. m.	Slight.	.....	8.15 p. m. Hb. 88%.	.....	9.00 p. m.	.....
21939	"	"	19	Dilatation of cervix. Appendectomy. Suspension of uterus.	2/29/16. 8.45 a. m.	Slight.	2/28/16. Hb. 93%. W. B. C. 9,920.	1.00 p. m. Hb. 105%. 8.00 p. m. Hb. 90%.	.....	7.00 p. m. Hb. 86%.	8.00 p. m. Hb. 90%.
21940	"	"	31	D. and C.	3/14/16. 8.20 a. m.	Very Slight.	3/12/16. Hb. 86%.	8.30 p. m. Hb. 91%.	8.15 p. m. Hb. 90%.	.....	.....
21941	"	"	32	Dilatation of cervix. Cauterization of cervix.	2/5/16. 9.45 a. m.	None.	2/4/16. 7.15 p. m. Hb. 97%.	7.15 p. m. Hb. 100%.	7.30 p. m. Hb. 100%.	7.30 p. m. Hb. 102%.	7.15 p. m. Hb. 105%.
22002	"	"	36	Double salpingectomy. Ligation of ovarian and internal iliac arteries. Percy cautery.	3/14/15. 2.00 p. m.	Very Slight.	3/13/16. Hb. 80%.	8.30 p. m. Hb. 80%.	8.15 p. m. Hb. 80%.	5.45 p. m. Hb. 75%.	.....
22073	"	"	55	Left S. O.	4/18/16. 12.10 p. m.	Slight.	4/17/16. Hb. 102%. W. B. C. 11,000.	8.00 p. m. Hb. 106%.	8.15 p. m. Hb. 108%.	.....	8.15 p. m. Hb. 108%.
22082	"	"	35	Hysteromyectomy. Hemorrhoidectomy.	4/17/16. 11.00 a. m.	Slight.	4/13/16. Hb. 110%. W. B. C. 8,000.	9.00 p. m. Hb. 125%.	7.45 p. m. Hb. 121%.	9.00 p. m. Hb. 125%.	.....
22023	"	"	24	Left Salpingectomy.	3/29/16. 9.30 a. m.	Very Slight.	3/28/16. Hb. 83%. W. B. C. 9,160.	7.30 p. m. Hb. 83%.	.....	8.30 p. m. Hb. 82%.	.....
21841	"	Black.	21	Double salpingectomy. Appendectomy.	1/13/16. 10.00 a. m.	Very Slight.	1/12/16. Hb. 68%. W. B. C. 8,000.	.....	Noon Hb. 65%.	7.00 p. m. Hb. 70%.	7.00 p. m. Hb. 72%. W. B. C. 16,000.
21831	"	White.	18	Appendectomy.	1/22/16. 9.30 a. m.	Very Slight.	1/20/16. Hb. 83%. W. B. C. 10,120.	7.00 p. m. Hb. 94%.	7.30 p. m. Hb. 95%.	7.30 p. m. Hb. 95%.	7.15 p. m. Hb. 96%.
21852	"	Black.	34	Hysteromyectomy.	1/20/16. 8.50 a. m.	Slight.	1/19/16. Hb. 74%. W. B. C. 4,000.	8.00 p. m. Hb. 77%.	7.00 p. m. Hb. 78%.	7.00 p. m. Hb. 75%.	8.00 p. m. Hb. 74%.
21947	"	"	31	Hysteromyectomy. Appendectomy.	1/15/16. 9.00 a. m.	Slight.	1/13/16. Hb. 75%. W. B. C. 15,600.	7.00 p. m. Hb. 85%.	7.00 p. m. Hb. 77%.	7.00 p. m. Hb. 72%.	8.15 p. m. Hb. 69%.
21974	"	"	36	Hysteromyectomy. Double salpingectomy. Left oophorectomy. Appendectomy.	3/14/16. Noon.	Slight.	3/13/16. Hb. 92%. W. B. C. 13,000.	7.30 p. m. Hb. 83%.	7.45 p. m. Hb. 79%.	5.30 p. m. Hb. 83%.	.....
22031	"	White.	47	Hysteromyectomy. Double S. O. Appendectomy. R. R. V. O.	3/27/16. Noon.	Slight.	2/15/16. Hb. 40%. R. B. C. 2,352,000. W. B. C. 1,000. 3/22/16. Hb. 50%. R. B. C. 3,800,000. W. B. C. 1,100. 3/25/16. 2 p. m. Hb. 54%. 3/27/16. Noon Hb. 53%.	1.30 p. m. Hb. 64%. 8.45 a. m. Hb. 68%.	.....	9.00 p. m. Hb. 53%.	.....

TABLE I.—HEMOGLOBIN IN CASES WITH VERY SLIGHT BLOOD LOSS AT OPERATION

5th Day	6th Day	7th Day	8th Day	9th Day	10th Day		Fluids Taken, Vomiting.	Remarks
.....	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	2/6/16. 11.00 a. m. Hb. 91%.	.....	Water well taken after operation. No vomiting.	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	7.45 p. m. Hb. 82%.	.....	.....	2/24/16. 7.45 p. m. Hb. 75%.	.....	.....	.....
.....	.....	.....	8.00 p. m. Hb. 83%.	.....	2/24/16. 7.30 p. m. Hb. 76%.	.....	No vomiting.	.....
8.00 p. m. Hb. 86%.	7.15 p. m. Hb. 89%.	.....	.....	.....	8.15 p. m. Hb. 87%.	2/27/16. 7.45 p. m. Hb. 92%.	.....	.....
.....	.....	.....	.....	.....	.....	.....	Water well taken after operation.	.....
7.15 p. m. Hb. 46%.	.....	.....	7.15 p. m. Hb. 43%.	.....	7.15 p. m. Hb. 50%.	3/7/16. 7.45 p. m. Hb. 48%.	Water not well taken after operation.	.....
7.45 p. m. Hb. 55%.	.....	.....	.....	7.45 p. m. Hb. 58%.	.....	2/27/16. 7.30 p. m. Hb. 61%.	3/10/16 10.30 a. m. Hb. 68%.	.....
.....	6.00 p. m. Hb. 78%.	.....	.....	.....	Hb. 88% W. B. C. 22,000	2/26/16. 8.30 p. m. Hb. 83%.	Water not well taken after operation. Slight vomiting.	Post-op. pelvic cellulitis.
.....	8.30 p. m. Hb. 80%.	.....	7.30 p. m. Hb. 91%.	.....	.....	.....	Water well taken after operation.	.....
7.30 p. m. Hb. 90%.	.....	.....	.....	.....	.....	.....	.....	Slight post-op. bleeding.
.....	.....	.....	.....	.....	.....	.....	Some vomiting.	.....
7.45 p. m. Hb. 75%.	.....	.....	7.45 p. m. Hb. 77%.	.....	.....	.....	Water well taken after operation.	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....
8.00 p. m. Hb. 112%.	.....	.....	.....	.....	.....	5/5/16. 8.00 p. m. Hb. 112% R. B. C. 6,120,000.	.....	.....
.....	.....	.....	8.45 p. m. Hb. 82%.	.....	.....	.....	.....	.....
7.00 p. m. Hb. 71%.	.....	.....	.....	.....	.....	1/28/16. Noon. Hb. 79%.	.....	.....
.....	.....	Noon. Hb. 93%.	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	Noon. Hb. 77%.	.....	.....	.....	.....
.....	7.00 p. m. Hb. 68%.	.....	.....	.....	.....	1/28/16. Noon. Hb. 89%.	.....	.....
7.30 p. m. Hb. 78%.	.....	.....	8.00 p. m. Hb. 77%.	.....	.....	.....	.....	.....
8.15 p. m. Hb. 55%.	.....	.....	.....	.....	8.15 p. m. Hb. 59%.	4/16/16. 7.30 p. m. Hb. 60%.	4/17/16. 9.00 p. m. Hb. 61%.	.....



TABLE II.—HÆMOGLOBIN IN CASES WITH MODERATE BLOOD LOSS

Gyn. No.	Female	Race	Age	Operation	Date	Blood Loss of Operation	Before Operation	After Operation. Day of Operation	2d Day	3d Day	4th Day
21647	"	White.	39	Curettage and cauterization of cervix.	11/2/15. 9.45 a. m.	Moderate.	11/1/15. Hb. 42%.	.....	Noon. Hb. 57%.	Noon. Hb. 54%.	.....
21799	"	"	14	D. and C.	1/30/16. 8.20 a. m.	Moderate.	1/19/16. Hb. 35%.	.....	Noon. Hb. 39%.	Hb. 31%.	7.45 p. m. Hb. 28%.
22615	"	"	39	Dilatation of cervix and manual removal of placenta.	11/25/16. 8.45 p. m.	Very slight. See "Remarks."	11/25/16. 8.30 p. m. Hb. 61%.	.....	7.45 p. m. Hb. 53%.	.....	7.45 p. m. Hb. 52%.
							W. B. C. 15,500. R. B. C. 3,880,000.		R. B. C. 3,600,000.		W. B. C. 9,200. R. B. C. 3,900,000.
21875	"	"	30	D. and C. R. R. V. O.	2/8/16. 8.20 a. m.	Moderate.	2/7/16. Hb. 96%.	7.45 p. m. Hb. 94%.	7.00 p. m. Hb. 89%.	8.00 p. m. Hb. 82%.	7.15 p. m. Hb. 82%.
							W. B. C. 12,520.				
21879	"	"	19	Hysterectomy (bi sector). Double salpingectomy. Right oophorectomy.	2/10/16. 11.55 p. m.	Moderate.	2/9/16. Hb. 93%.	8.45 p. m. Hb. 86%.	8.00 p. m. Hb. 83%.	7.45 p. m. Hb. 75%.	8.00 p. m. Hb. 70%.
							W. B. C. 8,200.				
21931	"	"	36	Hysteromyomectomy. Double salpingectomy. Appendectomy. Anterior and posterior colporrhaphy.	2/26/16. 11.25 a. m.	Moderate.	2/25/16. Hb. 57%.	2.00 p. m. Hb. 62%.	7.00 p. m. Hb. 54%.	8.00 p. m. Hb. 50%.	7.15 p. m. Hb. 46%.
							W. B. C. 9,400.	1 hr. after op.			
								7.45 p. m. Hb. 57%.			
21993	"	"	33	Hysteromyomectomy. Rt. salpingectomy. Appendectomy.	2/29/16. a. m.	Moderate.	2/28/16. Hb. 86%.	1.50 p. m. Hb. 79%.	7.45 p. m. Hb. 84%.	6.45 p. m. Hb. 77%.	7.00 p. m. Hb. 70%.
							W. B. C. 8,000.				
22046	"	"	47	Amputation cervix. R. R. V. O. Cauterization fissure in ano.	3/14/16. 8.45 a. m.	Moderate.	3/13/16. Hb. 86%.	8.00 p. m. Hb. 76%.	8.00 p. m. Hb. 70%.	6.00 p. m. Hb. 73%.	.....
							W. B. C. 5,360.				
22128	"	"	23	D. and C. Posterior vaginal celiotomy. Resection of left ovary.	5/13/16. 10.20 a. m.	Slight. See "Remarks."	5/13/16. 10.20 a. m. Hb. 100%.	8.00 p. m. Hb. 100%.	8.00 p. m. Hb. 89%.	.....	9.00 p. m. Hb. 88%.
							W. B. C. 9,500.				
20882	"	"	20	Panhysterectomy. Double salpingectomy. Left oophorectomy.	1/29/15. a. m.	Slight. 1/25/15. Hæmorrhage on wound.	Not made.	2/3/15. 8.30 p. m. Hb. 65%.	8.00 p. m. Hb. 35%.	Hb. 35%.	Hb. 39%.
								Very little bleed- ing. Severe bleeding.		No bleeding.	No bleeding.
20909	"	"	24	D. and C. cauterization cervix. R. R. V. O. Hæmorrhoidectomy.	1/28/15. a. m.	Slight. 2/6/15. 6.00 p. m. Severe hæmorrhage.	Not made.	2/3/15. 8.30 p. m. Hb. 86%.	Noon. Hb. 79%.	10.00 a. m. Hb. 55%.	Hb. 53%.
								No bleeding.	No bleeding.	No bleeding.	

TABLE II.—HÆMOGLOBIN IN CASES WITH MODERATE BLOOD LOSS

5th Day	6th Day	7th Day	8th Day	9th Day	10th Day					Fluid Taken, Vomiting	Remarks
Noon. Hb. 48%.	8.30 p. m. Hb. 50%.	.....	.....	8.30 p. m. Hb. 54%.	.....	11/12/15. Hb. 58%.	.....	.....	.....	.....	.....
7.15 p. m. Hb. 34%.	.....	.....	Hb. 42%.	.....	.....	.....	.....	.....	.....	.....	Pt. had constant bleeding for 2 mos. due to endometrial hyperplasia.
R. B. C. 3,864,000.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Water well taken after operation. No vomiting.	Began to bleed 2 days before op. Profuse hemorrhage 5 hrs. before op.
7.15 p. m. Hb. 77%.	7.30 p. m. Hb. 75%.	8.00 p. m. Hb. 73%.	7.00 p. m. Hb. 71%.	.....	.....	2/19/16. 8.15 p. m. Hb. 80%.	.....	.....	.....	Considerable vomiting day after operation.	.....
7.15 p. m. Hb. 73%.	.....	7.45 p. m. Hb. 74%.	.....	.....	.....	2/22/16. 7.45 p. m. Hb. 71%.	.....	.....	.....	.....	.....
7.30 p. m. Hb. 46%.	.....	7.30 p. m. Hb. 50%.	.....	.....	.....	3/7/16. 7.30 p. m. Hb. 54%.	3/25/16. 7.30 p. m. Hb. 55%.	.....	.....	Salt sol. 300 c. c. p. r. q. 4 h. day of operation. No vomiting.	.....
.....	8.30 p. m. Hb. 80%.	.....	8.00 p. m. Hb. 78%.	.....	.....	3/15/15. 7.45 p. m. Hb. 80%.	.....	.....	.....	.....	.....
8.00 p. m. Hb. 69%.	.....	.....	8.00 p. m. Hb. 70%.	.....	.....	.....	.....	.....	.....	Some vomiting 2 for 2 days. Post op.	.....
W. B. C. 7,800.	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
8.45 p. m. Hb. 68%.	.....	7.45 p. m. Hb. 90%.	.....	.....	.....	.....	.....	.....	.....	Very little vomiting. Post op.	Pt. says she had hemorrhage night of 5/12/16 and morning of 5/13/16.
10.00 a. m. Severe bleeding. 8.00 p. m. Hb. 41%.	8.00 p. m. Hb. 30%.	4.00 p. m. Hb. 30%.	7.00 p. m. Hb. 24%.	.....	2/16/15. 5.00 p. m. Hb. 30%.	2/19/15. 4.00 p. m. Hb. 22%.	2/23/15. Hb. 12%.	2/26/15. Hb. 18%.	2/28/15. Hb. 25%.	2/12/15. Indirect transfusion 300 c. c. 2/22/15. Salt sol. infusion.	Hemorrhage was from small vessel in vaginal vault.
No bleeding.	No bleeding.	R. B. C. 1,200,000. No bleed'g.	No bleeding.	No bleeding.	No bleeding.	No bleeding.	No hemorrhage.	No bleeding.	3/2/15. Hb. 35%.	.....	.....
Hb. 46%.	Hb. 50%.	.....	.....	Profuse hemorrhage.	2/19/15. Hb. 64%.	2/21/15. Hb. 68%.	.....	.....	.....	2 x 15. Salt sol. infusion 600 c. c.	Bleeding began 6/4/15. Not severe as 11/5 & 15/16 & 1917.

TABLE III.—HÆMOGLOBIN IN CASES OF SEVERE HÆMORRHAGE

Clin. No.	Female	Race	Age	Operation	Date	Blood Loss at Operation	Before Operation	After Operation, Day of Operation	2d Day	3d Day	4th Day	5th Day
19176	..	White	27	Dilatation and curet- tage. Rt. S. O.	1/7/13	.....	16.83 Hb. 46%.	.....	Hb. 39%.	.....	Hb. 37%.	.....
20088	..	..	25	Rt. S.	8/23/13	.....	8.23.03. Hb. 15%.	.....	.....	Hb. 16%.	.....	.....
20777	..	..	24	Resection of ut. interna tubule	11/3/14. 1.50 a.m.	.....	1.39.14. 1.4 a.m. Hb. 70% W. B. C. 20,000.	2.00 p.m. Hb. 50% W. B. C. 12,000.	Hb. 24%.	Hb. 30%.	Hb. 40%.	.....
22668	..	Black	21	Resection of left tube	12/2/15. 10.00 p.m.	.....	12/3/15. 9 p.m. Hb. 50% W. B. C. 10,600. R. B. C. 3,950,000.	11.00 p.m. Hb. 40% W. B. C. 20,000. R. B. C. 4,200,000.	11.30 a.m. Hb. 30% R. B. C. 2,440,000.	12.30 p.m. Hb. 30% R. B. C. 1,936,000.	12.30 p.m. Hb. 24% R. B. C. 2,120,000.	7.30 p.m. Hb. 24% R. B. C. 1,960,000.
22229	..	..	24	Pelvic puncture. Rt. salpingectomy	6/22/16. 10.00 p.m.	.....	6/19/16. Hb. 83% W. B. C. 9,100.	10.30 a.m. Hb. 70% W. B. C. 7,600. R. B. C. 4,332,000.	8.30 p.m. Hb. 55% R. B. C. 3,268,000.	9.00 p.m. Hb. 49% R. B. C. 3,268,000.	9.30 p.m. Hb. 50%.	9.30 p.m. Hb. 49%.
21760	..	White	31	Doubly-salpingectomy.	12/18/15. 11.00 a.m.	.....	12/17/15. Hb. 61% W. B. C. 13,600.	Noon. Hb. 61%.	4.00 p.m. Hb. 50%.	8.00 p.m. Hb. 40%.	.....	5.00 p.m. Hb. 50%.
19679	..	..	27	Hysteromyomectomy. Double S. O.	11/15/15. 11.00 a.m.	Severe hæmorrhage.	Not made.	7.45 p.m. Hb. 136%.	9.30 p.m. Hb. 122%.	7.00 p.m. Hb. 105%.	8.00 p.m. Hb. 98% W. B. C. 9,000. R. B. C. 5,000,000. Differential normal.	8.00 p.m. Hb. 90%.
22893	..	Black	20	Pelvic puncture. Hysteromyomectomy oblique. Double S. O.	2/16/16. Noon.	Severe hæmorrhage.	2/15/16. Hb. 73% W. B. C. 21,600.	2.30 p.m. 4 hr. after operation. Hb. 83% 7.30 p.m. Hb. 72%.	8.00 p.m. Hb. 47%.	8.00 p.m. Hb. 45%.	7.45 p.m. Hb. 56%.	.....
21775	..	..	32	Hysteromyomectomy. Double S. O.	3/13/16. 11.25 a.m.	Considerable.	3/11/16. Hb. 80% W. B. C. 7,200.	1.00 p.m. Hb. 50% 9.00 p.m. Hb. 68%.	7.30 p.m. Hb. 52%.	7.30 p.m. Hb. 46%.	5.30 p.m. Hb. 47%.	.....
21980	..	White	40	Parhysterectomy. Left S. O. R. R. V. O.	3/8/16. 11.50 p.m.	Considerable.	3/7/16. Hb. 40% W. B. C. 12,800.	Hb. 40%.	Hb. 35%.	.....	Hb. 53%.	.....
22924	..	Black	49	Hysteromyomectomy. Right S. O. Appendectomy.	4/1/16. 12.45 p.m.	Considerable.	3/31/16. Hb. 72% W. B. C. 7,200.	3.30 p.m. Hb. 64%.	3.00 p.m. Hb. 45%.	4.00 p.m. Hb. 52%.	.....	8.00 p.m. Hb. 50%.
22605	..	..	37	Nephrectomy, Left. Hæmorrhoidectomy.	2/16/16. 1.00 a.m.	Considerable.	2/1/16. Hb. 40% W. B. C. 5,200. R. B. C. 2,000,000.	Noon. Hb. 38% 7.30 p.m. Hb. 28%.	7.45 p.m. Hb. 29%.	3.00 p.m. Hb. 25% W. B. C. 2,320.	8.00 p.m. Hb. 24%.	.....
22328	..	White	37	Cancer, Zaino of cervix with high heat.	5/23/16. 11.00 a.m.	Considerable.	5/22/16. Hb. 49% W. B. C. 14,200.	2.00 p.m. Hb. 45% 7.30 p.m. Hb. 38%.	7.15 p.m. Hb. 31%.	7.15 p.m. Hb. 30%.	.....	.....
22880	..	..	23	Pelvic puncture. Exploratory laparotomy.	5/17/16. 12.30 p.m.	Considerable.	5/15/16. Hb. 95% W. B. C. 16,000. 5/16/16. 5 p.m. Hb. 86%.	2.00 p.m. Hb. 95% 9.00 p.m. Hb. 92%.	7.00 p.m. Hb. 81%.	8.00 p.m. Hb. 70%.	7.30 p.m. Hb. 68%.	8.30 p.m. Hb. 68%.
22192	..	Black	45	Parhysterectomy. Double S. O.	5/10/16. 10.30 a.m.	Severe hæmorrhage.	5/21/16. Hb. 70% W. B. C. 8,920.	1.00 p.m. Hb. 70% 7.15 p.m. Hb. 60%.	7.30 p.m. Hb. 42%.	7.53 p.m. Hb. 40%.	7.53 p.m. Hb. 41%.	.....
22541	..	White	31	Removal of retained placenta.	6/12/16. 4.00 p.m.	.....	5/30/16. Hb. 85% 6/12/16. 4.00 a.m. Hb. 51%.	4.30 a.m. Hb. 51% 8.00 p.m. Hb. 43%.	8.30 p.m. Hb. 30%.	8.00 p.m. Hb. 25%.	8.00 p.m. Hb. 31%.	.....
22563	..	..	41	Hysteromyomectomy. Double S. O.	11/4/16. 8.40 a.m.	Profuse hæmorrhage.	11/2/16. Hb. 68% W. B. C. 8,700.	4 hr. after operation. Hb. 75% R. B. C. 1,700,000.	4.30 p.m. Hb. 55% W. B. C. 11,600. R. B. C. 3,400,000.	7.00 p.m. Hb. 30%.	11.00 a.m. Hb. 39% R. B. C. 2,432,000.	.....
21747	..	..	28	Parhysterectomy. Double S. O.	5/8/16. 4 p.m.	Profuse hæmorrhage.	5/8/16. Hb. 80% W. B. C. 6,700.	.....	Hb. 70% W. B. C. 13,600.	.....	Hb. 60% W. B. C. 8,000.	Hb. 54%.
21321	..	..	33	Superficial hysteromyomectomy.	6/30/15. 11.00 a.m.	Slight hæmorrhage. See "Remarks"	6/29/15. 2.00 p.m. Hb. 68% 7.15 p.m. Hb. 45% 6/30/15. 10.45 a.m. Hb. 47%.	.....	Hb. 34%.	Hb. 31%.	Hb. 21%.	Hb. 41%.



TABLE III.—HEMOGLOBIN IN CASES OF SEVERE HÆMORRHAGE

6th Day	7th Day	8th Day	9th Day	10th Day						Fluid Taken, Vomiting	Remarks
.....	.....	.....	.....	.....	10/19/03. Hb. 45%.	.....	.....	.....	.....	.....	Ruptured tubal pregnancy. Abd. full of blood at op. Onset 1/3/03.
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Blood not removed from abd. cavity at operation.	Ruptured tubal pregnancy. Abd. full of blood at op. Onset 8/16/03.
.....	Hb. 45%.	.....	.....	.....	12/10/14. Hb. 55%.	12/13/14. Hb. 59%.	.....	.....	.....	Infusion of salt sol. 1000 c. c. begun at op. Water taken greedily after op. No vomiting.	Ruptured tubal pregnancy. About 2 litres blood in abd. Onset 12 hrs. before op.
.....	7.30 p. m. Hb. 29%. R. B. C. 2,300,000.	.....	.....	.....	12/16/16. 7.30 p. m. Hb. 42%. W. B. C. 8,200 R. B. C. 3,624,000.	.....	.....	.....	.....	Infusion of salt sol. 1500 c. c. begun at op. Water taken well after op. Very little vomiting.	Ruptured tubal pregnancy. Onset about 36 hrs. before op. Abd. filled with fresh blood.
.....	.....	9.15 p. m. Hb. 52%. R. B. C. 3,680,000.	.....	.....	.....	.....	.....	.....	.....	Infusion of salt sol. 2500 c. c. begun at op. 1 litre of salt sol. left in abd. cavity at end of op. No vomiting.	Tubal pregnancy ruptured 4 hr. before op. under ether. About 2 litres of fresh blood in abd. at op.
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Tubal pregnancy ruptured about 36 hrs. before op. Estimated 600 c. c. blood in abd. at op.
8.45 p. m. Hb. 88%.	5.45 p. m. Hb. 88%.	8.30 p. m. Hb. 95%.	8.15 p. m. Hb. 95%.	.....	11/26/15. 11.45 a. m. Hb. 95%.	.....	.....	.....	.....	Salt sol. infusion 1000 c. c. at op. Water well taken after op.	.....
.....	7.40 p. m. Hb. 68%.	.....	.....	.....	2/27/16. 7.30 p. m. Hb. 58%.	3/3/16. 7.30 p. m. Hb. 60%.	.....	.....	.....	Salt sol. infusion 1900 c. c. begun at op.	.....
7.15 p. m. Hb. 55%.	.....	.....	8.30 p. m. Hb. 53%.	.....	.....	.....	.....	.....	.....	Salt sol. infusion 1200 c. c. begun at op. Salt sol. p. r. 300 c. c. q. 4 h.	.....
Hb. 29%.	.....	Hb. 37%.	.....	Hb. 35%.	3/19/16. Hb. 39%.	3/21/16. Hb. 42%.	3/22/16. Hb. 49%.	3/23/16. Hb. 52%.	3/26/16. Hb. 52%. 3/30/16. Hb. 62%.	.....	.....
.....	7.45 p. m. Hb. 50%.	.....	.....	.....	4/11/16. 5.00 p. m. Hb. 58%.	.....	.....	.....	.....	.....	.....
.....	7.30 p. m. Hb. 29%.	8.00 p. m. Hb. 25%. R. B. C. 1,368,000.	.....	.....	2/26/16. Hb. 30%. W. B. C. 8,200 R. B. C. 1,228,000.	2/29/16. Hb. 30%.	3/3/16. Hb. 36%.	.....	.....	Salt sol. infusion 3100 c. c. during 24 hrs. after op.	.....
.....	.....	Hb. 37%. W. B. C. 13,000.	.....	.....	.....	.....	.....	.....	.....	Salt sol. 300 c. c. per rectum q. 4 h.	Died 6/1/16 from general peritonitis.
.....	8.00 p. m. Hb. 70%.	.....	.....	.....	6/4/16. Hb. 77%.	.....	.....	.....	.....	.....	.....
.....	.....	7.30 p. m. Hb. 50%.	.....	.....	6/5/16. Hb. 60%.	.....	.....	.....	.....	.....	.....
8.15 p. m. Hb. 33%.	.....	.....	.....	.....	6/23/16. Noon. Hb. 56%.	6/29/16. 8.30 p. m. Hb. 53%.	.....	.....	.....	Salt sol. infusion 2500 c. c. begun at op.	Bleeding began 6/11/16. 3.30 p. m. Severe hæmorrhage 6-12-16 1000 c. c. pack replaced.
4.30 p. m. Hb. 43%. R. B. C. 3,318,000.	.....	.....	.....	.....	11/14/16. 11.45 a. m. Hb. 46% W. B. C. 15,800 R. B. C. 3,208,000.	11/24/16. 3.30 p. m. Hb. 51% R. B. C. 3,618,000.	.....	.....	.....	Salt sol. infusion 840 c. c. on table. Salt sol. p. r. 1200 c. c. 1st 18 hrs. No vomiting.	.....
Hb. 62%.	.....	.....	Hb. 70%.	.....	5/21/15. Hb. 75%.	.....	.....	.....	.....	Salt sol. infusion on table 700 c. c. Salt sol. p. r. 300 c. c. q. 4 h. onward.	.....
Hb. 30%.	Hb. 34%.	Hb. 37%.	.....	Hb. 40%.	7/12/15. Hb. 41%.	7/15/15. Hb. 42%.	7/16/15. Hb. 48%.	7/18/15. Hb. 42%.	7/27/15. Hb. 50%. 7/19/15. Hb. 42%.	Salt sol. infusion 900 c. c. begun at op. Took water eagerly after op.	Some bleeding for 2 weeks. Severe hæmorrhage 7.45 a. m. 6/30/15.

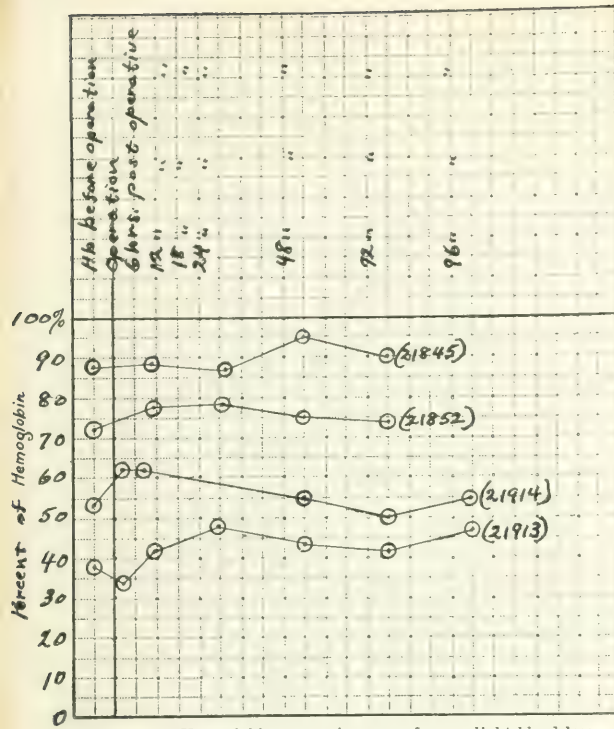


CHART I.—Hemoglobin curves in cases of very slight blood loss.

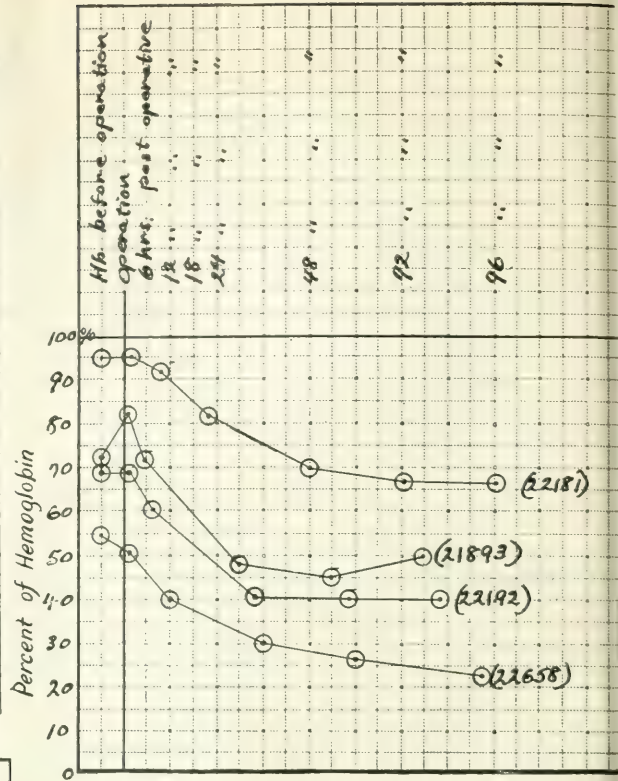


CHART III.—Hemoglobin curves in cases of severe hemorrhage.

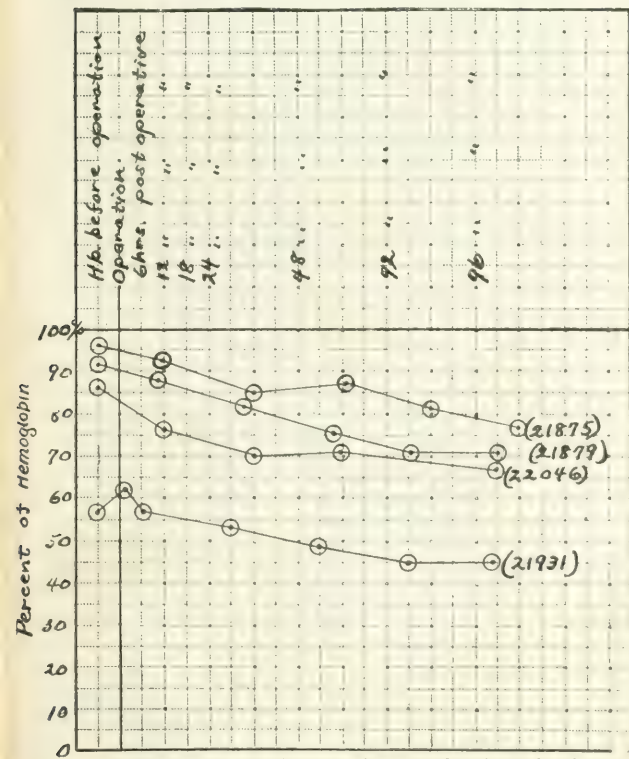


CHART II.—Hemoglobin curves in cases of moderate blood loss.

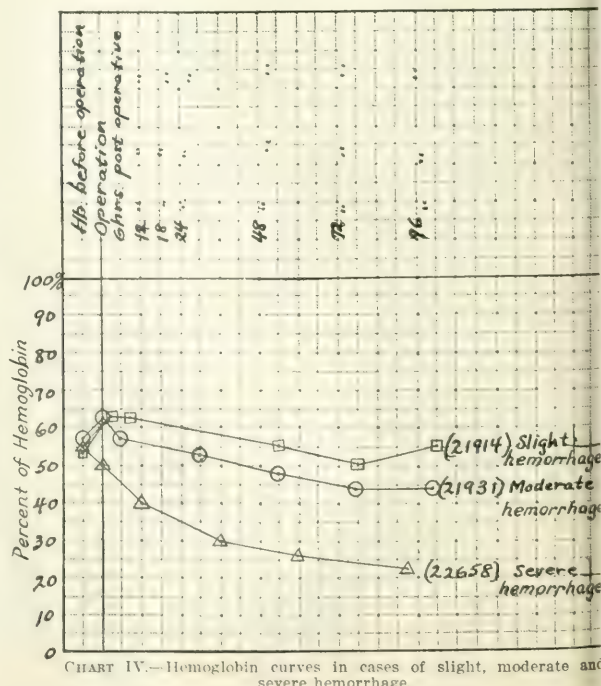


CHART IV.—Hemoglobin curves in cases of slight, moderate and severe hemorrhage.

## MEMBERS OF THE JOHNS HOPKINS HOSPITAL AND DISPENSARY STAFF ENGAGED IN MILITARY DUTY

DR. WILLIAM H. WELCH, Major, M. O. R. C., special duty, Surgeon General's Office.

DR. WINFORD SMITH, Major, M. O. R. C., special duty, Surgeon General's Office.

DR. THEODORE C. JANEWAY, Major, M. O. R. C., special duty, Surgeon General's Office.

DR. WILLIAM S. THAYER, Major, M. O. R. C., Red Cross Commission to Russia.

DR. JOHN M. T. FINNEY, Major, M. O. R. C., Chief of Surgical Staff, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. THOMAS R. BOGGS, Major, M. O. R. C., Chief of Medical Staff, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. GEORGE WALKER, Major, M. O. R. C., Adjutant and Surgeon, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. HUGH H. YOUNG, Major, assigned to British medical service.

DR. THOMAS B. FUTCHER, Consultant, Canadian Military Hospital, B. E. F., Orpington, Kent, England.

DR. WILLIAM S. BAER, Captain, M. O. R. C., Assistant Surgeon, (Orthopedic) U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. F. H. BAETJER, Major, M. O. R. C., on active duty, Johns Hopkins Hospital.

DR. CLYDE G. GUTHRIE, Captain, M. O. R. C., Assistant Physician, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. GEORGE J. HEUER, Captain, M. O. R. C., Assistant Surgeon (Brain Surgery), U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. WALTER A. BAETJER, Captain, M. O. R. C., Chief of laboratory staff, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. CHARLES BAGLEY, Captain, M. O. R. C., assigned to duty in Surgeon General's Office.

DR. BERTRAM M. BERNHEIM, Captain, M. O. R. C., Assistant Surgeon (Vein Surgery), U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. EVELETH W. BRIDGMAN, Captain, M. O. R. C., Assistant Physician and Registrar, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. JOHN STAIGE DAVIS, Captain, M. O. R. C., on active duty, Baltimore.

DR. WILLIAM A. FISHER, Captain, M. O. R. C., Assistant Surgeon, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. HARVEY B. STONE, Captain, M. O. R. C., Quartermaster, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. STANHOPE BAYNE-JONES, Captain, M. O. R. C., U. S. Army Medical Relief Corps, France.

DR. DAVID M. DAVIS, 1st Lieutenant, M. O. R. C., on active duty in France.

DR. H. C. SCHMEISSER, 1st Lieutenant, M. O. R. C., Pathologist, Albany Base Hospital.

DR. J. ALBERT CHATARD, 1st Lieutenant, M. O. R. C., on active duty, Fort McHenry.

DR. J. A. C. COLSTON, 1st Lieutenant, M. O. R. C., on active duty, Medical Department, British Army in France.

DR. FRANK A. EVANS, 1st Lieutenant, M. O. R. C., on active duty, Medical Department, British Army in France.

DR. JOHN H. KING, 1st Lieutenant, M. O. R. C., Assistant Physician, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. J. H. M. KNOX, JR., Red Cross Commission to France.

DR. E. A. PARK, Red Cross Commission to France.

DR. JOHN T. KING, JR., 1st Lieutenant, M. O. R. C., on active duty, assigned to J. H. H.

DR. WILLIAM L. MILLEA, 1st Lieutenant, M. O. R. C., on active duty, Camp Oglethorpe, Ga.

DR. HENRY R. SLACK, 1st Lieutenant, M. O. R. C., Assistant Surgeon (Laryngology), U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. HENRY L. SMITH, 1st Lieutenant, M. O. R. C., on active duty, Fort Oglethorpe, Ga.

DR. DANIEL D. V. STUART, Captain, M. O. R. C., on active duty, Washington, D. C.

DR. GEORGE L. STICKNEY, 1st Lieutenant, M. O. R. C., on active duty, Medical Department, British Army in France.

DR. ALAN C. SUTTON, 1st Lieutenant, M. O. R. C., on active duty, Medical Department, British Army in France.

DR. CHARLES A. WATERS, 1st Lieutenant, M. O. R. C., Roentgenologist, U. S. Army Base Hospital No. 18, American Expeditionary Force, France (Hopkins Base Hospital).

DR. CLARENCE A. NEYMANN, 1st Lieutenant, M. O. R. C., New York Psychiatric Unit.

Former members of the Hospital and Dispensary Staff who resigned during the past year to take up active military duty:

DR. EVERETT D. PLASS.

DR. DANIEL DAVIS.

DR. AUBREY T. MUSSEN.

DR. JOHN C. LYMAN.

DR. RAYMOND S. HUSSEY.

DR. VIRGIL P. W. SYDENSTRICKER.

DR. H. N. SHAW.

DR. L. R. WHARTON.

DR. CHARLES L. MCCARTHY.

DR. HOWARD E. ASHBURY.

DR. ERNEST S. DU BRAY.

DR. GEORGE R. DUNN.

DR. J. P. EDISON.

DR. R. W. HALL.

DR. W. D. JACK.

DR. U. R. MASON.

DR. T. L. SUTTON.

DR. C. E. SEVER.

DR. D. G. SMITH.

DR. H. C. SCHMEISSER.

DR. D. C. W. SMITH.

DR. H. W. REID.

DR. J. E. MOORE.

DR. M. K. MILLER.

DR. P. F. MCGUIRE.

DR. L. K. MCCAFFERTY.

DR. W. B. MARTIN.

DR. I. K. LOVETT.

DR. J. A. ETHERIDGE.

DR. H. C. BEAN.

DR. LAWRENCE REYNOLDS.

DR. G. A. STEWART.

DR. ROADES FAYERWEATHER.

DR. L. C. SPENCER.

DR. ELIZABETH HURDON.

DR. H. L. CECIL.

DR. N. M. KEITH.

DR. G. H. PRESTON.

DR. N. WORTH BROWN.



## NOTES AND NEWS

Dr. Dana W. Atchley is Instructor in Medicine and Instructor in Clinical Pathology, College of Physicians and Surgeons, Columbia University, New York City; and Assistant Physician, Presbyterian Hospital.

Dr. Frank C. Beall is Surgeon-in-Charge, the Johnson-Beall Hospital, Fort Worth, Texas.

Dr. Barney Brooks is Associate in Surgery, Washington University Medical School, and Visiting Surgeon, Barnes Hospital, St. Louis, Mo.

Dr. S. W. Budd is Associate Professor of Pathology and Associate in Medicine, Medical College of Virginia, Richmond, Va.

Dr. Walter C. Burket is First Lieutenant, Medical Reserve Corps. He is at present with Field Hospital No. 19, which is stationed at Fort Riley, Kansas.

Dr. Montrose T. Burrows is Associate Professor of Pathology and Acting Professor of Pathology, Washington University Medical School, St. Louis, Mo.

Dr. C. N. B. Camac is a Major in the Medical Reserve Corps, and Medical Chief of the Base Hospital, Fort McPherson, Ga. He is also Instructor in the School of Gas Defense, United States Army.

Dr. John R. Caulk is Associate in Clinical Genito-Urinary Surgery, Washington University; Assistant Surgeon to Barnes Hospital; Chief of Clinic, Genito-Urinary Department, Washington University Dispensary; Genito-Urinary Surgeon to St. Luke's Hospital, St. Louis, Mo.

Dr. John W. Churchman is Professor of Surgery, Yale University; Visiting Surgeon, New Haven Hospital; Acting Head of the Department of Surgery; Acting Chief Surgeon, New Haven Hospital and New Haven Dispensary.

Dr. S. W. Clausen is Resident Physician, Children's Hospital, St. Louis, Mo.

Dr. Henry Wireman Cook is Assistant in Medicine, the University of Minnesota.

Dr. C. D. Cowles, Jr., is Major in the Medical Corps, U. S. A., and is stationed at Fort Oglethorpe, Ga.

Dr. Arthur W. Elting is Major in the Medical Reserve Corps and Director of Base Hospital No. 33.

Dr. Clarence B. Farrar is Captain in the Canadian Army Medical Corps and is connected with the Psychiatric Military Hospital, Ottawa, Canada.

Dr. L. W. Gorham is Instructor in Medicine, Albany Medical College, and Assistant Attending Physician, Albany Hospital. He is a member of the Medical Reserve Corps and is Chief of Medical Service, Base Hospital No. 33.

Dr. R. L. Haden is Director of Laboratories, Henry Ford Hospital, Detroit, Mich.

Dr. C. W. Hennington is Major in the Medical Reserve Corps, and Assistant Director and Chief of the Surgical Service, Base Hospital No. 19.

Dr. James M. Hitzrot is Assistant Professor of Clinical Surgery, Cornell University Medical College.

Dr. August Hoch is editor of the Psychiatric Bulletin. Address: Montecito, Cal.

Dr. Samuel H. Hurwitz is Assistant Clinical Professor of Medicine, Medical Department, University of California.

Dr. Clarence B. Ingraham is Professor of Gynecology and Obstetrics, the University of Colorado. He is Captain in the Medical Reserve Corps and is stationed at present at Fort Riley, Kansas.

Dr. Theodore C. Janeway is a member of the General Medical Board of Council of National Defense.

Dr. Harry L. Langnecker is Passed Assistant Surgeon, U. S. N. R. F. He is Orthopedist to the Naval Base Hospital Unit No. 2.

Dr. D. Sclater Lewis is with No. 3 Canadian General Hospital, B. E. F., France.

Dr. Irving P. Lyon is Assistant Professor of Medicine, University of Buffalo, and Attending Physician, Buffalo General Hospital.

Dr. W. G. MacCallum is Professor of Pathology and Bacteriology, Johns Hopkins University, and Pathologist to the Johns Hopkins Hospital.

Dr. R. H. Major is Professor of Pathology, University of Kansas, Rosedale, Kansas.

Dr. Kenneth F. Maxcy is a member of the Medical Staff, Henry Ford Hospital, Detroit, Mich.

Dr. William B. McClure is Fellow in the Otho A. Sprague Memorial Institute, Chicago, Ill.

Dr. Carl R. Meloy is Director of Laboratories, the Grace Hospital, Detroit, Mich.

Dr. George R. Minot is Assistant in Medicine, Harvard Medical School, Assistant in Medicine, Massachusetts General Hospital, and holder of the Dalton Research Fellowship, Massachusetts General Hospital.

Dr. Charles F. Nassau is Assistant Professor of Surgery, Jefferson Medical College; Chief Surgeon, Frankford Hospital; Surgeon, St. Joseph's Hospital; Assistant Surgeon, Jefferson Medical College Hospital; and Consulting Surgeon, Pottstown Hospital, Pottstown, Pa.

Dr. C. D. Parfitt is Special Adviser in Tuberculosis, Toronto General Hospital.

Dr. H. W. Plaggemeyer is Instructor in Surgery, Detroit Medical College, Chief of Staff, Department of Urological Surgery, Grace Hospital, and Junior Attending Surgeon, Harper Hospital, Detroit, Mich.

Dr. J. P. Pratt is Assistant Surgeon, Henry Ford Hospital, Detroit, Mich.

Dr. D. Maxwell Ross is in charge of mental wards, 52d General Hospital, B. E. M. F., Salonika.

Dr. Peyton Rous is Associate Member, Rockefeller Institute for Medical Research, New York City.

Dr. Lewis A. Sexton is Superintendent, the Hartford Hospital, Hartford, Conn.

Dr. W. F. Shallenberger is Associate Professor of Gynecology, Emory University (Atlanta Medical College); Visiting Gynecologist, Georgia Baptist Hospital, and Assistant Visiting Gynecologist, Grady Hospital, Atlanta, Ga.

Dr. William Sharpe is Attending Neurologist to the Beth Israel Hospital, New York City.

Dr. Winford H. Smith is a member of the General Medical Board of Council of National Defense.

Dr. R. R. Snowden is a First Lieutenant in the Medical Reserve Corps. He is on duty in France with Base Hospital Unit No. 27.

Dr. A. R. Stevens is a member of the Medical Reserve Corps and is with the N. Y. Presbyterian Base Hospital Unit in France.

Dr. Solomon Strouse is Assistant Professor of Medicine, Northwestern University School of Medicine.

Dr. Martin B. Tinker is a Major in the Medical Reserve Corps. He is stationed at present at Fort Riley, Kansas.

Dr. Donald V. Trueblood is a First Lieutenant in the Medical Reserve Corps, and has been assigned to duty with the American Expeditionary Force in France.

Dr. P. S. Tucker is First Lieutenant, Medical Corps, U. S. A., and is stationed at Fortress Monroe, Va.

Dr. J. H. J. Upham is Professor of Medicine and Acting Head of the Department, Ohio State University School of Medicine, and President of the Ohio State Medical Board.

Dr. K. H. Van Norman is Assistant to Assistant Director Medical Services (A. D. M. S.) Military District No. 2; headquarters, Toronto.

Dr. L. M. Warfield is Assistant Superintendent, Milwaukee County Hospital, Wauwatosa, Wis., and Professor of Clinical Medicine at Marquette Medical School, Milwaukee, Wis.

Dr. Ernest M. Watson is Assistant Visiting Urologist to the Municipal Hospital and to the Erie County Hospital, Buffalo, N. Y.

Dr. Charles H. Watt is Surgical Director of the Union Hospital, Fall River, Mass.

Dr. Jerome P. Webster is First Lieutenant Medical Reserve Corps, and is stationed at Fort Benjamin Harrison, Ind.

Dr. William H. Welch is Director of the School of Hygiene to be established in connection with the Johns Hopkins University.

Dr. Milton C. Winternitz is Professor of Bacteriology and Pathology, Yale University School of Medicine, and Pathologist to the New Haven Hospital.

Dr. Paul G. Woolley is Mary M. Emery Professor of Pathology, University of Cincinnati. He is a Captain in the Medical Reserve Corps, and is stationed at Fort Oglethorpe, Ga.

Dr. J. Kent Worthington is Assistant in Urology, Indiana University School of Medicine; Assistant and Attending Urologist, City Hospital; and Attending Urologist, City and Babbs Dispensary. He is a Captain in the Medical Reserve Corps, and is stationed at present at Fort Benjamin Harrison, Ind.

Dr. Charles B. Wright is Chief of the Gastro-Intestinal Clinic, University Dispensary, and Assistant Visiting Physician, University Hospital, Minneapolis, Minn.

## BOOKS RECEIVED

*Diseases of the Genito-Urinary Organs and the Kidney.* By Robert Holmes Greene, A. M., M. D. and Harlow Brooks, M. D. Fourth edition, thoroughly revised. 1917. 8°. 666 pages. W. B. Saunders Company, Philadelphia and London.

*The Treatment of Tabetic Ataxia by Means of Systematic Exercise.* By Dr. H. S. Frenkel. Second revised and enlarged English edition by L. Freyberger, J. P., M. D. (Vienna), M. R. C. P. Lond., M. R. C. S. Eng. With 130 illustrations. 1917. 8°. 209 pages. P. Blakiston's Son & Co., Philadelphia.

*Dr. Lyman Spalding, the Originator of the United States Pharmacopæia.* Co-laborer with Dr. Nathan Smith in the Founding of the Dartmouth Medical School and its First Chemical Lecturer; President and Professor of Anatomy and Surgery of the College of Physicians and Surgeons of the Western District, at Fairfield, N. Y. By his grandson, Dr. James Alfred Spalding. 1916. 380 pages. W. M. Leonard, Boston.

*Operative Surgery of the Nose, Throat, and Ear.* For Laryngologists, Rhinologists, Otolologists, and Surgeons. By Hanau W. Loeb, A. M., M. D. in collaboration with Joseph C. Beck, M. D., George W. Crile, M. D., William H. Haskin, M. D., Robert Levy, M. D., Harris P. Mosher, M. D., George L. Richards, M. D., George E. Shambaugh, M. D., and George B. Wood, M. D. In two volumes. Volume II. Four hundred and seventy-six illustrations. 1917. 8°. 427 pages. C. V. Mosby Company, St. Louis.

*Asthma, Presenting an Exposition of the Nonpassive Expiration Theory.* By Orville Harry Brown, A. B., M. D., Ph. D., with a foreword by George Dock, Sc. D., M. D. Thirty-six engravings. 1917. 8°. 330 pages. C. V. Mosby Company, St. Louis.

*Experimental Pharmacology.* By Dennis E. Jackson, Ph. D., M. D. With three hundred and ninety original illustrations including twenty-four full-page color plates. 1917. 8°. 536 pages. C. V. Mosby Company, St. Louis.

*Impotency, Sterility and Artificial Impregnation.* By Frank P. Davis, Ph. B., M. D. 1917. 12°. 138 pages. C. V. Mosby Company, St. Louis.

*The Climate and Weather of San Diego, California.* Prepared under the direction of Willis L. Moore, Chief United States Weather Bureau. By Ford A. Carpenter, Local Forecaster. Illustrated with photographs and charts by the author and others. 1913. 16°. 118 pages. Published by the San Diego Chamber of Commerce.

*The Adventure of Death.* By Robert W. Mackenna. 1917. 12°. 197 pages. G. P. Putnam's Sons, New York and London.

*Acute Poliomyelitis.* By George Draper, M. D., with a foreword by Simon Flexner. With 19 illustrations. 1917. 8°. 149 pages. P. Blakiston's Son & Co., Philadelphia.

*Psychological Medicine.* A Manual on Mental Diseases. For Practitioners and Students. By Maurice Craig. Third edition. With 27 plates, some in colour. 1917. 8°. 484 pages. P. Blakiston's Son & Co., Philadelphia.

*Chemical and Microscopical Diagnosis.* By Francis Carter Wood, M. D. Third edition. With 194 illustrations in the text and 10 plates, nine of which are colored. 1917. 8°. 791 pages. D. Appleton & Company, New York and London.

*U. S. Department of Commerce, Bureau of the Census.* Mortality Statistics, 1915. Sixteenth Annual Report. Sam L. Rogers, Director. 1917. 707 pages. Government Printing Office, Washington.

*Saint Thomas's Hospital Reports.* New Series. Edited by Dr. J. J. Perkins and Mr. C. A. Ballance. Volume XLIII. 1914. 8°. 303 pages. 1916. J. & A. Churchill, London.

*Some Personal Recollections of Dr. Janeway.* By James Bayard Clark. 1917. 12°. 36 pages. G. P. Putnam's Sons, New York and London.

*American Association for Study and Prevention of Infant Mortality.* Transactions of the Seventh Annual Meeting, Milwaukee, October 19-21, 1916. 1917. 8°. 364 pages. Press of Franklin Printing Company, Baltimore.

*Notes on Galvanism and Faradism.* By E. M. Magill, M. B., B. S. Lond., D. P. H., R. C. S. I. (Hons.) With 67 illustrations. 1916. 12°. 220 pages. Paul B. Hoeber, New York.

*Urology.* Diseases of the Urinary Organs, Diseases of the Male Genital Organs, the Venereal Diseases. By Edward L. Keyes, Jr., M. D., Ph. D. With 204 illustrations in the text and 18 plates, four of which are colored. 1917. 8°. 908 pages. D. Appleton & Company, New York and London.

*Glaucoma.* A Handbook for the General Practitioner. By Robert Henry Elliot, M. D., B. S. Lond., Sc. D. Edin., F. R. C. S. Eng., etc. Lieut.-Colonel I. M. S. (Retired). 1917. 8°. 60 pages. Paul B. Hoeber, New York.

- The British Guiana Medical Annual.* Twenty-first year of issue for 1915. Edited by A. J. Craigen, M. B., Ch. B. (Aberdeen) and F. G. Rose, B. A., M. B., B. C. (Cantab.) M. R. C. S. L. R. C. P. 1916. 8°. 179 pages. Printed by "The Argosy" Company, Limited, Demerara.
- The Medical Association of the Isthmian Canal Zone.* Proceedings for the half year, January to June, 1916. Volume IX, part 1. 1917. 8°. 190 pages. The Health Department, Panama Canal Zone.
- Baltimore, Sub-Department of Health.* Department of Public Safety. Annual Report to the Mayor and City Council of Baltimore for the Fiscal Year Ended December 31, 1915. 1916. 8°. 348 pages. Meyer & Thalheimer, Baltimore.
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# BULLETIN

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## INTERSTITIAL PREGNANCY

By H. M. N. WYNNE,

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(From the Gynecological Department of The Johns Hopkins Hospital)

Ectopic pregnancy in the interstitial portion of the Fallopian tube is of especial interest on account of its infrequency and from the standpoint of diagnosis.

Several authors have given Pierre Dionis credit for being the first to describe a case of interstitial pregnancy, published in 1718 in his *Traité Général des Accouchements*. We find, however, that Dionis cites cases of tubal pregnancy he had seen with a drawing of one specimen, in which the foetus lay in the ampulla of the right tube, and discusses Mauriceau's famous case, in which he says the foetus was formed in the extremity of the tube which terminates in the uterus. ("Tous ceux qui ont examiné ce fait, sont convenus que cet enfant avait été formé dans l'extrémité de la rompe qui aboutit à la matrice, et ont été conformés dans l'opinion des oeufs.") According to Dionis, Mauriceau claimed that this foetus had been formed in the uterus and said that he would never accept any case of tubal pregnancy because they contradicted his theory and doctrine of generation.

Mauriceau's case, which he saw at autopsy with Benoit Vassal and others, was that of a woman of 32 years, who had given birth to 11 full-term babies, and during the third month

of her twelfth pregnancy died after having had violent abdominal pain, fainting attacks and convulsions for three days. This case was the basis of a long and heated discussion carried on between Mauriceau and Graaf, Dionis and other less celebrated men, who believed it, with Vassal, to be a tubal pregnancy. As we have seen, Dionis held that it was of the interstitial variety. The drawing published by Mauriceau illustrates very well a pregnancy in a rudimentary horn, although the author described it as a hernia of the uterine cornu. Mauriceau takes pains to explain that his drawing was the only correct one, as Vassal's was constructed from memory over a month after the autopsy and had been changed by others, who had copied it, to agree with their ideas.

Schmidt (1801) is generally credited with having reported the first authentic case. A treatise on this subject, with a discussion of four cases, was published in 1825 by Mayer. Brechet reported cases in 1826—Hedrick's, Bellemain's, Schmitt's and Dance's (Simon).

The first case reported by an American was by R. H. Fitz, of Boston, in 1875. The specimen, having been obtained at autopsy, was presented to him by A. T. Davison, who also

furnished the clinical history. Fitz published drawings and a careful description of the specimen after reviewing the literature, from which he accepted 18 cases. In 1885 Simon analysed the 40 cases reported to that time, nine of which he considered undoubtedly true interstitial, nine as doubtful and the remaining 24 as ectopic pregnancies of other types. Werth, in 1904, considered 40 cases above criticism, but Weinbrenner in the same year believed that five of these were not to be allowed.

Since these reviews, additional cases have been collected from the literature or reported by the following: Finsterer, 17 cases in 1908; Lequeux, 12 cases in 1911; Schenk, 19 cases in 1912, and Farrar, 10 cases in 1914. Of these reports, there are several overlapping, as Schenk gives seven previously mentioned by Lequeux and Farrar, one of which was reported by Schenk. We have not attempted to review the individual cases cited by these several authors. If all were to be allowed, the total to 1914 is 85 cases. The subject has been discussed very thoroughly, and references to a fairly large literature have been given by the authors mentioned above.

#### OCURRENCE

The percentage of interstitial pregnancies in all types of ectopic gestation is usually stated as 3 per cent. This is based on the work of von Rosenthal, who collected from the literature 1324 cases of all types before 1896 and 40 cases of interstitial pregnancy reported during the same time. According to the more recent works of Werth and Weinbrenner, there were considerably less than 40 cases of true interstitial pregnancy at that time.

We believe that a more accurate method of determining the percentage is to total several series from the larger clinics, in which careful differential diagnoses have been made. These figures are as follows:

	Cases
Baculescu reported one interstitial in a series of.....	58
Finsterer reported one interstitial in a series of.....	133
Kastaneff (Wasten's clinic) reported eight interstitial in a series of .....	335
Krivsky reported two interstitial in a series of.....	223
Lahostky reported two interstitial in a series of.....	150
Mandl and Schmidt reported no interstitial in a series of....	77
Martin reported one interstitial in a series of.....	77
Tait reported one interstitial in a series of.....	100
Werth reported no interstitial in a series of.....	120

In this clinic there have been 304 cases of ectopic pregnancy operated on, only two of which can be classed as interstitial. In a total of 1547 cases of ectopic pregnancy, there are 18 cases of interstitial pregnancy (1.16 per cent).

#### CLASSIFICATION

The classification and differentiation of interstitial pregnancy have been thoroughly discussed by Weinbrenner, Kohlmann and Lequeux. The implantation of the ovum must be in the interstitial portion of a tube, including diverticula from the tube, extending into uterine muscle. But in view of the fact that the development of the embryo may change anatomical relations to some extent, various classifications have been

proposed; that of Klebs will cover most of the conditions found at operation and is as follows:

- (1) Graviditas utero-interstitialis,
- (2) Graviditas tubo-interstitialis,
- (3) Graviditas interstitialis propria.

#### DIAGNOSIS

The distinguishing details of the differential diagnosis between this type and pregnancy occurring in other portions of the tube or in a rudimentary horn may be found tabulated in Farrar's paper.

Virchow noted that the round ligament is always outside of the gestation sac. The insertion of the round ligament is usually lateral and inferior or anterior and inferior to the gestation sac. Glaesmer says that in his case the round ligament was medial to the sac and discusses this phase of the diagnosis at length. Lequeux says that the variations in the insertion of the round ligament are due to the variety of implantation and to the evolution of the ovum. The relation of the proximal end of the tube to the gestation sac is subject to variation also. The tube is usually inferior, but can be more or less lateral according to the development of the ovum. Von Rosenthal believed that the tube was always inserted into the inferior border of the gestation sac.

According to several more recent papers Ruge's sign is not always present. This sign, as stated by Simon, is that the distance between the insertions of the tube and round ligament is increased and the adnexa of the affected side are higher than on the other side, owing to the increase in size of the pregnant horn and some rotation of the uterus following this asymmetrical development. A positive diagnosis of interstitial pregnancy before operation is, we believe, very unlikely. Kelly described a type of apical pregnancy which may be mistaken for the interstitial variety, in which there is often severe pain; and on examination the softening and enlargement of the uterus is confined to one apex, even as late as the fifth month, but these terminate normally. He also states that they may be interstitial pregnancies with the ovum lodged very near the uterine cavity and become intrauterine secondarily, although he does not interpret them as such.

There are also early isthmal pregnancies developing very close to the uterine cornu, difficult to diagnose at operation. In this clinic the diagnosis at operation in seven cases has been cornual pregnancy, but on careful histological study only two have proven to be interstitial in origin.

Pregnancy in one horn of a bicornuate uterus may in certain cases present a serious difficulty in making the differential diagnosis, as also can a small myoma in one cornu or a unilateral cornual abscess, especially when associated with the retained membranes of an early abortion.

Sturmdorf made a diagnosis of ectopic pregnancy on the right side, but at operation the right-sided mass proved to be a tubo-ovarian abscess, and in the left cornu, which was thought to be normal, there was an early interstitial pregnancy.

Robin's case was diagnosed ectopic pregnancy or acute appendicitis, and an exploratory McBurney incision made to deter-

mine the exact condition. In the case reported by Schenk, the pre-operative diagnosis was correct and the pre-operative diagnosis in Schumann's case made by Hirst proved to be right.

Lewers considers persistent amenorrhœa a very important sign in the differential diagnosis. Our investigation of 36 cases showed that amenorrhœa was persistent in 12, the periods were quite regular in two and irregular bleeding occurred in 22 cases, although it was very slight in five of these.

Siefert claims that no interstitial pregnancies are seen after the sixth month; but Ferguson reports a case which he considered primarily interstitial and secondarily abdominal, operated on by him at term, but his report is too incomplete to establish the diagnosis above criticism. Cases have been reported in which an 8-month fœtus was found by Kupferberg and a 7-month fœtus by Glaesmer. Pegataz performed a supravaginal hysterectomy for myomata on a patient who had shortly before given birth spontaneously to a 6½-month fœtus. On examining the uterus, he found the placenta in the interstitial portion of the tube.

Beckmann and Siefert believe that perforations always occur on the posterior convex surface of the gestation sac. In 20 cases in which we have found the site of rupture mentioned, it is described as on the posterior surface in eight, on the posterior superior surface in five, on the posterior lateral surface in one, on the superior surface in three, on the superior anterior surface in two, and on the anterior surface in one. This last-mentioned case was exhibited in 1903 by Seitz.

Rupture generally occurs during the first half of pregnancy. There is at present a considerable number of patients in the literature who were operated on before rupture had occurred. The statistics are as follows:

Month	Ruptured			Cases since 9/8	Operated on	
	Simon	Werth	Finisterer		Ruptured	ruptured
1.....	..	1	..	2	2	2
1-2.....	..	3	2	4	9	4
2.....	2	4	3	5	14	4
2-3.....	..	6	1	2	9	1
3.....	5	4	1	3	13	2
3-4.....	..	2	..	1	3	2
4.....	2	4	..	..	6	4
4-5.....	..	4	..	..	4	..
5.....	..	3	1	1	5	..
5-6.....	..	1	..	..	1	..
6.....	..	..	..	..	..	..
7.....	..	..	..	2	2	..
8.....	..	..	..	1	1	..

These statistics show that the most usual time for rupture is during the second and third months. The statistics of Baart de la Faille, Henning and Parry (quoted from Eckert) show that rupture occurs most frequently between the third and fifth months. The tables given above, however, include cases that have been more strictly criticised than those of the authors mentioned, as well as the recent cases.

There have been two other cases reported as unruptured, but the age of the fœtus was not stated. The total number of cases up to 1917 is about 91, and 21 of these were unruptured (about 23 per cent.).

The ages of the patients in 38 cases are as follows:

Years	No. of patients	Years	No. of patients
21.....	1	31.....	2
24.....	2	32.....	1
25.....	4	34.....	4
26.....	1	35.....	3
27.....	3	36.....	2
28.....	6	39.....	1
29.....	3	40.....	2
30.....	2	41.....	1

The decade between 25 and 35 years shows the greatest number of cases.

In a series of 42 cases the numbers of pregnancies prior to the interstitial pregnancy are as follows:

No. of pregnancies	No. of cases	Miscarriages
0.....	5	
1.....	13	1 (induced).
2.....	11	2 pts. had 1 each, and 1 pt. 2 (induced).
3.....	5	1 patient had 1.
4.....	4	1 patient had 2.
5.....	2	
9.....	1	7 miscarriages.
16.....	1	2 miscarriages.

The time elapsing after the last pregnancy before the interstitial pregnancy in 19 cases was as follows:

Time	No. of cases	Time	No. of cases
2 months.....	1	4 years.....	1
7 months.....	1	5 years.....	1
11 months.....	1	6 years.....	1
1 year.....	2	7 years.....	1
16 months.....	1	11 years.....	1
2 years.....	1	13 years.....	1
2½ years.....	1	14 years.....	1
3 years.....	4		

## CAUSE

Conditions that bring about the abnormal embedding of the ovum in other portions of the tube are doubtless responsible for the occurrence in this portion as well. Dionis (1718) argued that the interstitial part of the tube should be the seat of tubal pregnancy more often than any other part of the tube; owing to its smaller calibre, however, there are fewer folds of the mucosa in this section and the lumen is less encroached upon by inflammatory changes than at any other part of the tube. Frankl considers the presence of diverticula of the utmost importance as a cause of interstitial pregnancy.

We shall not repeat the numerous theories advanced to explain the cause of tubal pregnancy, as they have been discussed in many of the papers on this subject.

Scott believes previous curettage responsible for some cases, but this theory is difficult to uphold, as, in curettage of the uterine cavity, the apices are practically never injured; this can be demonstrated by opening a uterus removed immediately after a careful curettage.

Nache attempted to sterilize a woman by making a wedge excision of the tubes from the uterus, but four months later was obliged to perform a laparotomy for an interstitial pregnancy.



The right tube and ovary were absent and the right uterine cornu was the seat of an interstitial pregnancy in a case operated on by Andrews.

#### TREATMENT

The first operation for interstitial pregnancy was performed on October 15, 1893, by Traub, who did a supravaginal hysterectomy, and on October 23, 1893, Lawson Tait operated on a case by incising the sac, evacuating the contents and draining. Since that time the treatment of choice has been operative, as soon as a diagnosis has been made which indicated operative interference, and in the great majority of cases this has been done after rupture of the sac. Immediate operation is most important in this type of ectopic pregnancy on account of the enormous hæmorrhage that almost always follows rupture and the small chance that the bleeding will cease before the patient is moribund.

A great variety of operations have been done for this condition. In 66 cases the following operations have been performed:

VAGINAL	
Panhysterectomy .....	1
Wedge excision of cornu.....	1
ABDOMINAL	
Panhysterectomy .....	2
Panhysterectomy with double salpingo-oöphorectomy..	1
Supravaginal hysterectomy .....	17
Supravaginal hysterectomy with drainage.....	1
Resection of uterine cornu.....	8
Resection of uterine cornu with salpingectomy.....	1
Resection of uterine cornu with salpingo-oöphorectomy.	1
Resection of uterine cornu and digital cleaning of uterine cavity from above.....	1
Resection of uterine cornu and curettage of uterine cavity from above.....	1
Excision of uterine cornu with salpingo-oöphorectomy.	2
Excision of gestation sac.....	9
Excision of gestation sac with salpingectomy.....	1
Excision of gestation sac with salpingo-oöphorectomy.	4
Wedge excision of cornu.....	8
Wedge excision of cornu with salpingo-oöphorectomy.	2
Incision of gestation sac, evacuation of contents and drainage.....	1
Cleaning out sac and suture of wound.....	2
Cleaning out sac and suture of wound, with drainage through the uterus.....	1
Dilatation and curettage followed by laparotomy, with incision into sac, evacuation of contents, uterine cavity opened, suture of wound, myomectomy.....	1
Dilatation of cervix and removal of intrauterine ovum with forceps, followed by laparotomy with a wedge excision of the cornu, uterine cavity not opened....	1

The abdominal route has been used in all but two cases and undoubtedly is the best. The type of operation must be selected to fit the emergency, as in the more advanced cases hysterectomy is usually preferred and in the earlier cases excision of the cornu with suture usually can be done more quickly. Speed is almost always to be considered, as the majority of these patients are in bad condition.

Schurmann's patient was treated expectantly for three weeks, when, on account of continued pain, the uterus was explored digitally, the gestation sac broken into, a 4-month foetus with the placenta was removed and the uterine cavity curetted.

Farrar, following Kelly's suggestion, after having opened the abdomen and finding no rupture, curetted the gestation sac from below, guarding against puncture with one hand in the abdomen.

The interval between the onset of acute symptoms and operation has been as follows:

Ward's case .....	4 hours.
Polak's case .....	4-5 hours.
Glaesmer's case .....	6½ hours.
Siefert's case .....	7 hours.
Kohlmann's case .....	11 hours.
J. H. H. Gyn. No. 20777.....	12 hours.
Nacke's case .....	24 hours.
Lequeux's case .....	24 hours.
Funke's (Kühlmann) case .....	36 hours.
Andrew's case .....	3 days.
Weinbrenner's case (1).....	14 days.
v. Holst's case .....	14 days.
Muret's case had ruptured some time before and closed off by intestinal and omental adhesions; the foetus was four and one-half months old.	
Cullingworth's case ruptured at the third month; the operation was done five months after conception; the foetus had been dead some time before the operation.	
Treub's case ruptured at the third month, secondary abdominal pregnancy developed, foetus measuring 41 cm. when removed.	
Farrar's case unruptured; severe vaginal hæmorrhage a few hours before operation.	
J. H. H. Gyn. No. 15342, unruptured; hæmorrhage through tube into abdomen; onset 16 days before operation.	

#### PROGNOSIS

All authors agree that the prognosis in this type of ectopic pregnancy is extremely grave. Werth in a series of 31 operated cases found four deaths; Finsterer, two deaths in 17 cases; Schenk, four deaths in 19 cases (no operation in two cases). Lequeux reports two deaths in five cases (no operation in one case) and Farrar 10 cases with one death, while in the five undoubted cases since the latter's paper there were no deaths. (Two of Schenk's cases included in Lequeux's report (one death) and one of Farrar's cases reported by Schenk.) In 82 operative cases there were 10 deaths or a 11.9 per cent mortality with operation.

Prior to 1893, all the cases in the literature had been found at autopsy. Of the nine undoubted cases analysed by Simon in 1885, the time from the onset of symptoms due to rupture until death was less than 12 hours in two cases, less than 24 hour in four cases, 27 hours in one case and 15 days in one case.

Wagner's patient (Case III) died 17 hours after an acute onset, while being prepared for operation. A 6-week foetus was found at autopsy.

Kupferberg's patient died 48 hours after an acute onset, while being prepared for operation. At autopsy an 8-month foetus was found.

Eckert's patient died 15½ hours after an acute onset. A 3-month fetus was found at autopsy.

Bar and Bufnoir's patient died five days after an acute onset. At autopsy a fetus weighing 1025 grams was found. It had evidently been alive until the time of rupture.

The cause of death (post-operative) in nine cases was stated as follows:

Bonnaire and Brac's patient was about six weeks pregnant. The cervix was dilated, the uterine cavity curetted and an intra-uterine injection of iodine given, followed by death 45 minutes later. At autopsy no cause for death found.

Funke's (Kühlmann) patient ruptured at the third month; the first acute symptoms had appeared 35 hours before operation. She was in shock when operated upon, and died one and one-quarter hours later. Supravaginal hysterectomy was performed.

Glaesmer's patient had ruptured probably six and one-half hours before operation. She was in shock when operated upon, and died three hours later. A 7-month dead fetus was removed at operation by panhysterectomy with bilateral salpingo-oöphorectomy.

Koblanck's (Opitz) patient was in shock when operated upon, and died a few hours later. A 1 to 2-month pregnancy was removed by a wedge excision of the cornu with suture.

Kynock's patient was in poor condition when operated upon, although the sac had not ruptured. A 4-month pregnancy was removed by supravaginal hysterectomy. The patient died three days later from hemorrhage from the cervical stump.

Olhausen's (Opitz) patient was in shock when operated upon, and died a few hours later. A 1 to 2-month pregnancy was removed by a wedge excision of the cornu with suture.

Raschkes' patient had ruptured when three and one-half months pregnant. A resection of the uterine cornu was done, and the patient died eight days later with symptoms of a general peritonitis.

Siefert's patient had ruptured seven hours before operation. A 2-month pregnancy was removed by resection of the uterine cornu, and death occurred 12 hours later from shock.

Weinbrenner's patient (Case II) underwent a resection of the uterine cornu for a 4-month infected pregnancy; the fetus was macerated. Death occurred three days later from general peritonitis.

#### REPORT OF CASES FROM THE LITERATURE

Since the publication of Farrar's paper, there have been 11 cases published, of which only three have been reported in full, with pathological and histological descriptions. A thorough microscopic study is necessary in many cases to prove the diagnosis beyond criticism, although only a small number have been studied carefully in this way. Eckert states that up to 1901 only three cases had been submitted to microscopic studies, Ullesko-Stroganowa's, Leopold's and Raschkes'.

The undoubted cases are Mangiagalli's (fully reported by Colombino in 1914) and Popoff's two cases (in 1914).

Probable cases have been reported by

Czyzewicz, 2 cases, 1914. (No illustrations; no pathological report.)  
Gibson, 1 case, 1914. (No illustrations; incomplete pathological report.)

Heyman, 1 case, 1915.

Kastaneff, 4 cases, 1914. (No illustrations; no microscopic report.)

Kohlman, 1 case, 1916. (No pathological report.)

Leonormant & Hartmann, 1914, 2 cases in a series of 37 tubal pregnancies (descriptions incomplete).

Oastler, 2 cases, 1915. (No illustrations; no pathological report.)

Viannay, 1 case, 1913. (No illustrations; no microscopic report.)

Vineberg, 2 cases, 1915. (No illustrations; no pathological report.)

One case was operated on by himself and one case he saw at autopsy.

#### REPORT OF CASE

GYN. No. 20777.—The patient was a white woman, 24 years old, married five years, who had had a normal labor and puerperium three years before and had had no miscarriages. Six years before admission she had had an attack of abdominal pain diagnosed as appendicitis, but had not been operated upon for it. The past history was otherwise negative.

Her last regular period began August 1, 1914; since that time amenorrhœa had persisted. She considered herself pregnant.

At 1 p. m., November 29, 1914, she fell down stairs, and at 1.30 p. m., while attending to her household duties, she was seized with violent general abdominal pain and lay down on the floor, where she remained until carried to bed. The pain continued very severe all the afternoon and at 5 p. m. she vomited. She noticed that her abdomen was becoming larger and was very tender. A physician was called to see her and brought her to the hospital with a diagnosis of an acute ruptured appendix. At 11.55 p. m., November 29, 1914, she was admitted to the hospital.

*Physical Examination.*—The patient is a well-nourished and well-developed woman in much pain. The skin and mucous membranes are extremely pale; the skin is cold and covered with sweat; the pulse is 160, small and weak; the temperature (rectal) 99°F. The abdomen is distended, tense, very tender, and movable dullness is demonstrable.

*Diagnosis.*—Ruptured extra-uterine pregnancy.

The patient was taken to the operating-room at once and prepared for operation. Under ether anesthesia the pelvic examination revealed a uterus twice the normal size. A small nodule was felt in the right uterine cornu and a soft mass in the right fornix (suggesting clot). W. B. C. 20,000. Hb. 70 per cent (Sahli).

*Operation.*—At 1.30 a. m., November 30, 1914, by Dr. J. C. Neel, Resident Gynecologist.

When the abdomen was opened through a midline incision below the umbilicus a large amount of fluid blood and fresh clots escaped (estimated at two liters). A nodule measuring 2.5 cm. in diameter was seen in the right uterine cornu, on the posterior surface of which there was a perforation 1 cm. in diameter, through which placental tissue bulged. There was no active bleeding. The attachment of the round ligament was anterior to the gestation sac. A few fine adhesions were found about the right adnexa; the left tube and ovary were normal.

The uterine cornu and a small portion of the right tube were rapidly resected, the uterine cavity was opened and cleaned out with the finger. The wound was then sutured with catgut and the raw area covered by suturing over it a fold of the round ligament. Fluid blood and clots were quickly cleaned out of the abdominal cavity and the abdomen was closed in layers.

A subcutaneous infusion of normal salt solution was started during the operation and continued in the ward, 1500 cc. in all being given.

The patient made a rapid recovery and was discharged from the hospital in good condition, December 13, 1914.

The hæmoglobin curve in this case is interesting.

On admission	11/30/14, 1 a. m.	Hb = 70% (Sahli)	W. B. C. 20,000.
	11/30/14, 3 p. m.	" = 50% (Sahli)	W. B. C. 12,000.
	12/1/14.....	" = 34% (Sahli)	
	12/2/14.....	" = 30% (Sahli)	
	12/3/14.....	" = 40% (Sahli)	
	12/6/14.....	" = 45% (Sahli)	
	12/10/14.....	" = 55% (Sahli)	
	12/13/14.....	" = 59% (Sahli)	

Somewhat similar hæmaglobin curves have been found in a series of cases of acute hæmorrhage followed by Dr. Dunn and myself during the past two years.

*Specimen from Gyn. No. 26777. Anatomical No. 1188.*—The specimen consists of the right uterine cornu and 1.5 cm. of the tube. It measures  $3.5 \times 2.5 \times 2.5$  cm. The posterior superior wall bulges out, and in the most prominent area there is a perforation measuring 1 cm. in diameter, through which a mass of chorionic villi protrudes. At the proximal end of the specimen there is a small area of endometrium, measuring 8 mm. in thickness. The portion of tube accompanying the specimen measures 5 mm. in diameter.

A longitudinal section of the specimen shows a gestation sac measuring 2 cm. in diameter, which is filled with blood-clot, and chorionic villi, surrounded by uterine muscle which, between the gestation sac and endometrium, measures 2 cm.

*Microscopic Study.*—There is a marked decidual reaction of the endometrium, areas of markedly hypertrophied uterine glands (spongy layer) and other areas of slightly hypertrophied glands. There is some infiltration with polymorphonuclear and mononuclear leucocytes. The vessels are gorged with blood.

The cells of the myometrium are hypertrophied. The gestation sac is surrounded by uterine muscle which, over the posterior wall, is thinned out to 2 mm. in thickness (the perforation was above this section). The muscular wall lies between the gestation sac and the proximal section of the isthmus of the tube.

The peritoneal surface is covered with a single layer of cells, varying from the cuboidal to flat types, with light-staining cytoplasm and uniformly dark-staining nuclei lying about the center of the cells.

Two vessels in the muscular layer show marked hypertrophy of the endothelium. Syncytial cells have invaded the muscle and opened up blood spaces. A thin layer of decidual cells can be seen in some areas, but there is no continuous decidual layer. No tubal mucosa can be found. Masses of chorionic villi in blood-clot are present; some villi are edematous and are covered by the syncytial layer only, while others have well preserved Langhans and syncytial layers. No amnion was found. The fetus was not found.

A cross section of the tube between the uterine cavity and the gestation sac shows strands of two layers of epithelial cells in apposition for the most part, but in one or two areas these two layers are separated by small spaces showing that the lumen has been compressed. The cilia can be seen on these cells. The tissue between these strands of epithelium is composed of a very vascular connective tissue infiltrated with small round cells. At one edge of the tube there is a small, irregularly shaped lumen. At the edge of the circular muscle layer there are several spaces apparently due to splitting of the muscle.

The isthmus of the tube shows no evidence of inflammatory reaction. The folds of the mucosa are normal; cilia are present, there is no hypertrophy of the muscle and no decidual reaction can be found.

It seems probable that in this case the ovum was arrested in the interstitial portion of the tube, owing to this inflammatory condition just described.

*Gyn. No. 15342.*—The patient was a negro 35 years old, married 18 years, who had one full-term child 11 years before and had had no miscarriages. The labor and puerperium were normal. There was no history suggesting pelvic inflammatory disease. Menstruation had been normal. The last period had begun, November 16, 1908, and had continued the usual four days. No periods had been missed and there was no history of intermenstrual bleeding.

*Present Illness.*—At 7 p. m., November 23, 1908, she was seized with a severe cutting pain in the R. L. Q. of the abdomen, which lasted until 4 a. m., November 24, 1908. A similar attack had occurred on December 1, 1908, accompanied by nausea and vomiting, and again, on December 3, 1908, she had had an attack localized

in the umbilical region, accompanied by nausea and vomiting, and the patient fainted while walking to her bed. For the five days before admission she had had burning with frequency and difficulty on voiding. For two weeks there had been a foul, irritating vaginal discharge, not bloody. She had felt giddy frequently and had been confined to bed most of the time after onset.

*Physical Examination.*—On admission, December 6, 1908. Temperature  $99^{\circ}$ . Pulse 96, good quality. The mucous membranes are pale. The breasts contain colostrum. There is a small umbilical hernia and a right inguinal hernia; otherwise the abdomen is normal.

*Pelvic Examination.*—There is no evidence of infection of Bartholin's glands or of the urethra. The cervix is enlarged but otherwise normal. The fundus is in ante-position and movable. The adnexa are adherent, thickened and tender. There is a small nodule in the right uterine cornu.

December 9, 1908. Examination under ether anaesthesia discloses no abdominal masses. A slight chocolate-colored discharge is present. The cervix is enlarged but firm. The fundus is about normal in size; it is adherent in mid-position and there is a soft mass in the right uterine cornu. The ovaries are adherent.

*Diagnosis.*—Chronic pelvic inflammatory disease. (Extrauterine pregnancy was not suspected.)

December 9, 1908. Operation by Dr. Casler. Resident Gynecologist.

When the abdomen was opened through a midline incision below the umbilicus, a large quantity of old, dark, clotted blood was seen. At the right uterine cornu there was a soft cystic tumor, the size of a small lemon. The right tube was practically normal except for a slight oozing from the fimbriated extremity. The left adnexa were adherent. The insertion of the round ligament was anterior and lateral to the tumor. The right tube and uterine cornu were resected, the wound was sutured with catgut and the raw area covered by suturing a fold of the round ligament over it. A cigarette drain was placed through the posterior vaginal vault. During the operation the specimen was ruptured and a very small deformed fetus escaped.

The abdomen was irrigated with normal salt solution and closed in layers. The patient made a satisfactory recovery and was discharged, December 23, 1908.

*GYN. PATH. No. 14277.*—The specimen consists of a Fallopian tube and cornu of the uterus. The tube measures 6 cm. in length, with an average diameter of 9 mm.; it is somewhat nodular, the fimbriated extremity is open. There are no adhesions over the surface. The cornu measures  $4 \times 3 \times 3$  cm.; there is an opening on the upper surface  $1 \times 1.5$  cm., with a cavity  $2 \times 1.5$  cm. which is lined with a smooth greyish tissue. The wall of this cavity is 8 mm. thick and is evidently a cavity in which pregnancy has existed. The opening between the tube and cornu is patent. (The specimen has been preserved in 50 per cent alcohol. The photograph was made in 1915 and shows where the original blocks for microscopic study were cut. A number of other blocks have been cut since.)

*Microscopic Study of Specimen (Path. No. 14277).*—The inner lining of the cavity consists of the amnion, which is well preserved. Immediately below the amnion lies the chorion; in most instances the villi show more or less degeneration, but in some Langhans and the syncytial layers stain clearly. Between the villi there are fibrin and collections of leucocytes (largely polymorphonuclear cells). Syncytial cells can be seen invading the muscular wall and there are several areas of decidual cells, although there is no uniform layer of decidua.

In the region of the gestation sac there is no evidence of any tubal mucosa or of any uterine glands.

The gestation sac is completely surrounded by muscular wall, except over the posterior superior surface, where there is an opening in the sac. About 1 cm. lateral to this opening, a section shows the uterine wall completely destroyed and villi extending through



the gap, which measures 2 mm. in width. In the muscular layer of the posterior wall there are two cavities, lined with a single layer of epithelium, varying from a low cuboidal to the rather high columnar type; the cells are large, having a dimly staining or clear cytoplasm and large, oval nuclei containing from one to four deep staining nucleoli; no cilia can be seen on these cells. There is no special arrangement of muscle around these spaces. The tube proximal to the gestation sac cannot be found. There is no endometrium.

A section through the uterine cornu distal from the gestation sac shows the interstitial portion of the tube and three other cavities, one of which is similar to those described in the posterior wall; the other two are larger and are lined with a single layer of poorly staining epithelium, varying from almost flat to the low columnar type. These cavities are filled with blood pigment and debris of cells. The interstitial portion of the tube shows some hypertrophy of the epithelium. There is no definite evidence of inflammatory reaction.

In the isthmus of the tube, vessels are gorged with polymorphonuclear leucocytes and there is some polymorphonuclear infiltration outside the longitudinal muscle layer. The folds of the tube are not thickened and are not adherent; the cilia of the epithelial cells can be seen; the lumen is clear.

In the ampulla of the tube there is a small amount of free blood. Many vessels are filled with polymorphonuclear leucocytes, but there is no leucocytic infiltration of the tube walls and no other evidence of inflammatory reaction.

No decidua reaction outside the region of the gestation sac can be found.

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## TRANSPLANTATION OF THE TRACHEA

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With the purpose in view of the possible utilization of a tracheal transplant in human cases in which a portion of the trachea has been resected on account of malignant disease, as suggested by Dr. William S. Halsted, I undertook to study the transplantation of the trachea in dogs. And furthermore, as a preliminary step in this problem, it seemed clear that an im-

portant factor in the success of the tracheal transplants would be the determination of the sterility of the trachea at different levels.

A review of the literature showed the rather extensive work that has been done on the healing of tracheal wounds after resection and the use of various grafts for closing tracheal

defects. The work began in 1831, when Dupuytren first studied the plastic closure of the tracheal wall. In 1855 DeCubach attempted to cover tracheal defects with a flap of tissue; Schüller in 1880 described the healing process of the tracheal wounds; and it has been well known that the trachea could be completely divided and the ends successfully resutured in animals and human cases, following a report of the work of Gluck and Zeller in 1881, and the later reports of Küster, von Colley, Förderl, von Eiselberg, Jones, Keene, Mesnard, von Hacker, Frankenberger, Frank, Gluck, Koenig, Kander, von Navratil, Nowakowski, Turner, Alagna and Sarguon. Complete annular segments of the trachea, varying in length from 2 to 5 cm., were excised and the remaining tracheal stumps successfully sutured by Küster in 1885, Nowakowski in 1909, and Alagna in 1913. By far the greater portion of study has been applied to the treatment of tracheal fistulae, by using various materials for transplantation. In 1893 Photiades and Lardy used a skin-periosteal cartilaginous flap from the clavicle; while Schimmelbusch in 1893, Koenig in 1897, Aue in 1900, and Kusnetzow in 1909, reported using such a flap from the sternum; a skin and thyroid cartilage flap was used by Koenig in 1896 and by Wiessinger in 1906; a rib cartilage flap by von Mongold in 1899, and by Mehues in 1903; a periosteal-cartilage flap from the tibia by von Navratil; a silver wire net by Grosse in 1901; free fascia transplants by Kirschner in 1910; and fascia lata by John Staige Davis in 1911. Later reports of studies with the use of fascia have been made by Koenig, Hohmeier, Kostenko, Rubasckew, Levit, Lucas, Kirschner, Münnich, Jacquin and Malan. Various methods of using skin flaps from the neck have been described by Trnka and von Masek. In 1893 Photiades and Lardy used a rubber tube surrounded by a skin flap to take the place of a tracheal defect following a resection of the trachea for cancer. Lazarraga, Firmin-Gaston Rouzoul, Baracz and Bruwer have gone over part of the literature upon plastic surgery of the trachea. But searching through the literature revealed no other aid in the present problem until it had been completed, when the reports of three different authors were found which have been completely abstracted in the following paragraph: Mesnard in 1901 reported before the Anatomical Society of Paris that four days previously he had begun the study of transplantation of complete segments of the trachea in two dogs, and that he would show the results at the next meeting of the society; but there was no subsequent statement of the outcome of this attempt that could be found. The second experimenter was Caldera, who, in 1913, reported three groups of experiments on rabbits. He successfully resutured with catgut the divided trachea, and at post-mortem examination found a well healed wound that seemed a clearly marked annular scar which was infiltrated with calcareous salts. In the second group of experiments Caldera made tracheal transplants of complete segments, 1.5 cm. in length, with the result that one rabbit had post-operative symptoms of stenosis for 16 days, and post-mortem examination after 20 days showed a heavy annular deposit of calcium salts, while another rabbit showed a calcareous infiltration of the cicatrix without stenosis. In

the third group of experiments he made tracheal transplants of segments of similar size after preserving them for 24 and 48 hours in sterile Ringer's solution at 37° and 20° C., respectively. He reported at the end of 20 days a satisfactory clinical and anatomical result and a moderate calcareous infiltration of the cicatrix without stenosis. In conclusion he stated, without having made any cultural examinations that one could find, that the bacteria which were habitually present in the trachea had become attenuated in virulence, so that therefore they did not constitute a danger at the time of the operation. Furthermore, he added that the anastomotic union of the trachea took place by connective tissue, which was infiltrated with lime salts. He mentioned no bibliography and only briefly described his specimens, which were not reproduced in the article. Finally, Zucardi-Merli in 1914 reported an experiment upon dogs in which he planned to repeat the work that Caldera did upon rabbits. Using the same technique he tried fresh tracheal transplants consisting of four cartilagenous rings, with the result that a left lateral stricture was formed that did not produce symptoms during life. In the case of the transplants preserved for 48 hours in Ringer's solution and placed in a different-sized animal, he claimed to have obtained after 20 days a satisfactory union without stenosis. He then repeated the fresh tracheal transplants of the same diameter of the trachea and employed more accurate technique, with the result that all were failures. He stated that the stenosis, which some observers have obtained after simple resection and suture, might be due to the contraction of an organized blood clot about the trachea, as a result of the imperfect approximation of the bleeding edges. He did not fully describe the specimens, which were not reproduced in the article.

On account of the splendid results obtained in several of the cases of auto-tracheal transplants in dogs, it was deemed advisable to report the following experiments which seemed to divide themselves into two classes; the main division consisted in the auto- and iso-transplantation of complete annular segments of the trachea in dogs; and a subordinate division, which was undertaken as a preliminary step to the main problem, consisted in the determination of the sterility at different levels of the trachea of the cat.

The experiment to determine the sterility of the trachea was as follows: Under ether anesthesia and after sterilizing the operative field thoroughly with alcohol, the trachea was exposed from the larynx to its bifurcation. Blood for cultures was taken from the carotid artery. Four sets of sterile instruments were used in obtaining the different specimens, as follows: One to expose the trachea and to remove wound muscle as control culture of the operative technique; and other sets to remove the trachea at three different levels; that is, at the bifurcation, midway up, and just below the larynx, respectively. These tracheal rings and pieces of muscle were placed in broth, in Ringer's solution, in blood, and in 1/100000 aqueous bichloride solution. Some of the cultures were kept on ice and others at 37° C. Approximately 60 cultures were thus made. All of the control cultures and all the cultures that were kept on ice and later placed in the thermostat remained free from bacterial

growth, as did also the cultures that were kept at 37° C., except for a cloudy growth after 48 hours in one of the broth cultures from the trachea near the hilus of the lung, which contained a small piece of a lymph gland that probably accounted for the growth. The stained smear of this culture showed a Gram-positive coccus that was not in chains. The remaining cultures of the trachea near the hilus of the lung showed no growth.

With a knowledge of the preliminary facts as just stated concerning the sterility of the trachea, the following experiment in the auto-transplantation of the trachea in dogs was made. The animals were kept under ether anaesthesia by mouth or through a tracheotomy wound. A midline incision was made from the larynx to the suprasternal notch and the muscles separated down to the pretracheal fascia. This fascia contained numerous blood vessels, which in part supplied the circulation to the intercartilaginous portions of the trachea. These vessels were ligated and divided only over that portion of the trachea which was to be transplanted. A second important blood supply of the trachea was furnished by a vessel upon either side of the trachea and parallel with it; this was ligated just at the point where the trachea was to be divided, in order to preserve the circulation of the trachea to the very line of incision. After careful attention to the blood supply, a segment of the trachea, composed of from three to nine cartilaginous rings in length, was completely separated by transverse incision and removed, thus assuring complete absence of blood supply to the transplant. This auto-transplant was then replaced and sutured end-to-end by using three equidistantly placed interrupted black silk sutures, which picked up the perichondrium and cartilage without penetrating the entire tracheal wall. The silk was threaded on fine, curved French needles which were fastened in a needle-holder, and very small delicate forceps were used to steady the tissues in order to avoid trauma. One short continuous black silk suture was placed in the fibro-elastic posterior wall of the trachea. Both ends of the transplant were sutured in the same way. The incised end of the transplant was just approximated to the cut surface of the trachea, without tension or overlapping. No disfigurement to the normal contour of the trachea was caused by the transplant, and no air escaped through the line of anastomosis when it was completed. One long heavy black silk tension suture (refer to photograph) was placed in the anterior surface of the trachea from above to below the transplant in order to relieve tension upon it during the process of healing. The perichondrium of the tracheal rings proved to be the strong layer of closure. The pretracheal fascia was approximated with a continuous silk suture; the muscles were brought together in the midline; and the skin was tightly closed with a continuous subcuticular fine black silk suture. A collodion gauze dressing was applied.

The operative technique in the cases of the iso-tracheal transplants was similar to that just stated for the autotransplants. Both animals were operated upon at the same time and the tracheal transplants were interchanged. Intratracheal anaesthesia was administered through a separate tracheotomy

wound which was located below the region of the transplant. It was an interesting fact that the tracheal segments from the different-sized animals were readily adapted in size to one another because of the anatomical fact that the cartilaginous portion of the tracheal rings was not complete and the posterior wall was formed of fibro-elastic tissue.

All animals recovered promptly from anaesthesia and operation. The skin wounds healed *per primam*. After operation some of the animals (C<sub>7</sub>, C<sub>1</sub>, C<sub>6</sub>, D<sub>1</sub>, D<sub>2</sub>) had an hoarse voice, a dry cough, and a rather stiff neck, which, when walking, they would occasionally shake from side to side, especially in the case of the dogs with the long transplants. Although otherwise their general condition remained very well, yet after from one to three weeks they developed marked symptoms of tracheal obstruction with dyspnea, and died. Autopsy revealed a normal esophagus and lungs, and a stricture of the trachea at the site of the transplant. Only one animal (C<sub>4</sub>) developed a purulent infection at the site of the transplant, together with a complicating bronchitis and pneumonia which caused death in four days after the operation. In these unsuccessful cases, the dogs with the short tracheal transplants lived from one to two weeks, while the animals with the long transplants lived approximately three weeks. The cases of iso-tracheal transplants resulted in death with symptoms similar to the unsuccessful cases of auto-transplants, and autopsy showed normal lungs with stricture of the trachea at the region of the transplant.

The microscopical studies of sections made through the anterior and posterior walls of the strictures showed it to consist of a mass of granulation tissue, in the deeper layers of which there were pieces of poorly staining cartilage that were in the process of destruction. Many long and short chains of a rather large, thick bacillus and numerous scattered cocci were present. The mucous lining was usually absent and the normal relationship of the tracheal layers was destroyed.

The successful transplant cases (C<sub>3</sub>, C<sub>5</sub>, C<sub>8</sub>) showed no symptoms and gave every evidence that they were as healthy and normal as before operation. At the time when these dogs (C<sub>3</sub>, C<sub>5</sub>, C<sub>8</sub>) were sacrificed in order to observe the experimental results, hair had grown out and covered the neck of the animal, completely hiding the white line of the operative incision. The neck showed nothing unusual in appearance, and upon palpation the structures of the neck felt normal and were freely movable. Upon exposing the trachea it was found normally mobile, without adhesions, and one could make out by gross examination no reaction in the tissues or structures about the site of the transplant. The healing was so satisfactory that the location of the anastomosing silk suture was the best guide to the transplant. There was no disfigurement to the normal contour of the trachea, as can be seen in the photographs which were taken by J. A. Martin, of the Johns Hopkins Hospital. The color, consistency, and shape of the cartilage and tissues forming the transplant seemed normal, like that in the unoperated portion of the trachea. The inside of the trachea was smooth and normal throughout its length. The life of these perfect transplants (C<sub>3</sub>, C<sub>5</sub>, C<sub>8</sub>), that is, from



the date of the operation until the animals were sacrificed, was 62, 54, and 36 days, and the segment transplanted was composed of three, four, and seven cartilaginous rings, respectively.

Upon histological examination of the anterior and posterior walls of the trachea, the tissues of the transplant appeared so normal that it was difficult to locate the point of anastomosis except by the presence of the suture or by the knowledge of the location of the section in the original specimen. The layers had their normal relationship. The epithelium was everywhere present, although it was not as high at

little indenture on the left side of the transplant which proved, on opening the trachea, to be a moderate lateral stricture.

Therefore, from the above facts one might say: (1) that according to the studies with cultures, the trachea was practically in all cases sterile from the larynx to the hilus of the lung; (2) that transplant C<sub>6</sub>—54 days, was an example of a perfect auto-tracheal transplant; (3) that in the successful cases the healing took place by the normal layers of the tracheal wall and not by fibrous cicatrix; (4) there was no infiltration with calcareous salts; (5) that the strictures resulted from an infection which was caused by the organisms that were observed

#### RESULTS OF TRACHEAL TRANSPLANTS—ALL ANIMALS REPORTED

No. of medium or large sized dog	Date of operation, 1917	No. of tracheal rings transplanted	Auto- or iso-transplant	Healing	Post-operative symptoms	End of experiment	Duration of experiment	Result
C <sub>1</sub>	March 31.	3	Auto.	Per primam.	Slight hoarseness, slight stiffness of neck. Tendency to shake neck. After 10 days difficulty in breathing began and became gradually fatal.	Died, April 14.	14 days.	Stricture of trachea. Lungs OK.
C <sub>2</sub>	April 17.	3	"	"	Slight dry cough for a few days.	Sacrificed, June 19.	63 days.	Slight stricture on left side of trachea. Lungs OK.
C	April 18.	3	"	"	(None).	Sacrificed, June 19.	62 days.	Transplant fine. Lungs OK.
C <sub>1</sub>	April 19.	3	"	Infection at site of transplant.	Difficulty in breathing. Rapid, short respiration. Some prostration at end.	Died, April 23.	4 days.	Breaking down of transplant; bronchitis; pneumonia.
C <sub>2</sub>	April 26.	4	"	Per primam.	(None).	Sacrificed, June 19.	54 days.	Transplant perfect. Lungs OK.
C <sub>2</sub>	April 26.	8	"	"	Neck somewhat stiff. Shakes head and neck. Voice hoarse. Some difficulty in respiration.	Sacrificed, June 19.	24 days.	Stricture of trachea. Lungs OK.
C <sub>1</sub>	May 8.	9	"	"	"	Died, June 2.	25 days.	Stricture of trachea. Lungs OK.
C <sub>2</sub>	May 11.	7	"	"	(None).	Sacrificed, June 19.	36 days.	Transplant fine. Lungs OK.
D <sub>1</sub>	May 25.	6	Iso.	"	Difficulty in respiration. Dry cough.	Died, June 2.	8 days.	Stricture.
D <sub>2</sub>	May 25.	6	"	"	Difficulty in respiration. Dry cough.	Died, June 1.	7 days.	Stricture.

the point where the incision had been made. The anastomosis was formed by the tissues of the different layers themselves and not by connective tissue. There was no scarring or infiltration with lime salts. There was no reaction in the tissues except for a beginning giant-cell development about the sutures which took place for the purpose of absorbing the silk. The cartilage of the transplant stained the same and, as nearly as one could tell, resembled that of the untransplanted portion of the trachea. No bacilli nor cocci could be seen anywhere in the sections.

A fourth case (C<sub>2</sub>) had a slight dry cough for a few days after operation, which cleared up. Otherwise, dog (C<sub>2</sub>) seemed healthy and normal and when sacrificed 63 days after operation, the trachea looked to be in good condition except for a

in the histological sections; (6) that iso-tracheal transplants resulted in stenosis.

Furthermore, one might offer an explanation or possible interpretation of several facts which became evident in the course of these experiments. In the first place, the stricture of the trachea that resulted in the unsuccessful cases was probably due to the low-grade infection that was not sufficiently virulent to cause the skin wounds to break down or to infect the lungs. The organisms might have gotten into the trachea with the air while the animals breathed through the tracheotomy wound at the site of operation. A second point that perhaps might be mentioned was that the infection which appeared in the one tube containing the piece of lymph gland, during the study of the sterility of the trachea, emphasized the point

that lymphatic vessels and glands which must be cut across in a clean wound should receive careful sterilization either with the cautery or by carbolic-alcohol technique, just as any other infected material. This would be especially true in a case where the glands and vessels drained regions that were known to be badly exposed to infection. Such technique would only require a more accurate knowledge of the lymphatic structures and their drainage, and cutting these infected lymphatic vessels and glands might explain some of the unexpected infections which develop in clean wounds.

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instance, *Staphylococcus aureus* failed to produce amyloid in the rabbit (Petroni, Tarchetti); living *B. pyocyaneus* and *B. coli* in the rabbit (Nowak); suppuration in the rabbit (Gianturco); *B. dysenteriae* in the horse (Pease, Pearce); oil of turpentine in the dog (Krawkow).

It may be seen from the foregoing that although many different substances have been injected over long periods into several different types of animal, no constant success has attended upon these experiments. In this study, animals were chosen from the list of those already used with success, which were suitable for the study of the blood pressure, and the methods of injection employed were those that had been most frequently successful. Goats, dogs and rabbits were used, *Staphylococcus* being injected into the rabbits and goats and oil of turpentine into the dogs. The use of *Staphylococcus aureus* was based on Krawkow's method, and cultures in bouillon, from three to seven days old, were injected under the skin of the back, twice a week, in increasing doses starting with 0.3 or 0.5 c. c. New strains of *Staphylococcus* were used whenever they could be obtained from human autopsies or elsewhere. Instead of the living cultures given subcutaneously, killed cultures of *Staphylococcus aureus* were injected intravenously into a number of rabbits. The 48-hour bouillon culture was killed by heating in a water-bath at 60-62° C. for 20 minutes, and injections were made twice a week in increasing doses. The method of using turpentine in the dogs was based upon that of Lubarsch. Beginning with doses of 0.5 c. c., it was injected subcutaneously into the back of the dog, the dose being increased gradually and marked suppuration maintained.

The experiments were as follows:

I. Three goats injected with living cultures of *Staphylococcus aureus* over periods of 225, 245 and 253 days received respectively 629, 719 and 819 c. c. of the culture. At autopsy they showed no amyloid in any of their organs.

II. Six dogs received subcutaneous injections of turpentine twice weekly in doses increasing from 0.5 to 4 c. c. over periods which

varied from 16 to 272 days. The total amounts of turpentine received by the dogs which lived a long time were 44 c. c. during 165 days; 72 c. c. during 189 days and 94.5 c. c. in one dog that lived 272 days. Although suppuration was continuous and some of the dogs showed albuminuria and casts, the autopsy revealed no trace of amyloid in any of the organs in any case.

III. Thirty rabbits received subcutaneous injections of bouillon cultures of living *Staphylococcus aureus* twice a week in doses beginning with 0.3 c. c., but increased gradually until doses of 20-25 c. c. were being given in many cases. The rabbits lived for different lengths of time after the beginning of the experiment but some survived large doses for 90-173 days, receiving a total, in some cases, of as much as 370 c. c. of the culture. A few showed albuminuria but not one developed a trace of amyloid in the organs which were thoroughly studied at autopsy in each case.

IV. Twelve rabbits were similarly treated with intravenous injection of killed *Staphylococcus aureus*, one surviving 249 days and receiving 441.8 c. c. of the suspension. Others survived for periods varying from 23 to 173 days and received corresponding doses of the suspension. Two of them showed albuminuria but the organs at autopsy were, in every case, devoid of amyloid and indeed showed little departure of any kind from the normal.

In the goats, there were no significant changes in the kidney except that in one case there was a certain amount of epithelial necrosis probably associated with the terminal peritonitis. In the dogs after turpentine injections there were generally no special changes in the kidneys, although some showed hyaline glomeruli, epithelial degeneration and infiltration with wandering cells.

Similar changes were found in the kidneys of a majority of the rabbits and some presented even extensive scarring. Albuminuria and casts were found throughout the experiment in many cases. Focal necroses—abscesses in the liver and abscesses in the spleen and lung—were also found.

Changes in the rabbits treated with killed staphylococci were much less marked than in those treated with the living organism but were of a similar character. These changes are evidently due to the direct action of the injurious agent employed in the experiment, since the animals were normal

TABLE I—GOAT

Date	Experiment No.	Animal No.	Staphylococcus aureus	Age of culture	No. of c. c. injected	Dose (in c. c.)	Length of life after first injection	Length of life after last injection	Method of injection	Urinary changes	Amyloid
1/28/16	I	1	Living	3-7 days	719.0	0.5-32.0	245 days	1 day	Subcutaneously	Albuminuria for a few days	Neg.
2/4/16	II	2	"	3-7 "	819.5	0.5-30.0	253 "	1 "	"	Neg.	"
2/18/16	III	3	"	3-7 "	629.3	0.5-30.0	225 "	1 "	"	"	"

TABLE II—DOG

Date	Experiment No.	Animal No.	No. of c. c. of turpentine injected	Dose (in c. c.)	Length of life after first injection	Length of life after last injection	Method of injection	Urinary changes	Amyloid
1/7/16	IV	1	24.0	1.0-4.0	48 days	1 day	Subcutaneously	Neg.	Neg.
1/14/16	V	2	18.5	0.5-4.0	33 "	1 "	"	Albuminuria, casts	"
2/25/16	VI	3	2.0	0.5-1.0	16 "	4 "	"	Neg.	"
3/28/16	VII	4	72.0	0.5-4.0	189 "	2 "	"	"	"
4/27/16	VIII	5	94.5	0.5-4.0	272 "	2 "	"	Slight albuminuria	"
7/13/16	IX	6	44.0	0.5-4.0	165 "	2 "	"	Albuminuria	"

TABLE III—RABBIT

Date	Experiment No.	Animal No.	Staphylococcus aureus	Age of culture	No. of c.c. injected	Dose (in c.c.)	Length of life after first injection	Length of life after last injection	Method of injection	Urinary changes	Amyloid
1/3/16	X	1	Living	5-7 days	26.1	0.3-6.0	44 days	1 day	Subcutaneously	Albuminuria, casts	Neg.
1/19/16	XI	2	"	3-7 "	25.3	0.3-5.5	41 "	1 "	"	"	"
2/11/16	XII	3	"	3-7 "	41.8	0.3-6.5	43 "	2 "	"	"	"
3/8/16	XIII	4	"	3-7 "	1.8	0.3-1.0	10 "	2 "	"	Neg.	"
3/13/16	XIV	6	"	3-7 "	70.3	0.3-10.0	78 "	3 "	"	Albuminuria	"
4/11/16	XV	8	"	3-7 "	17.3	0.3-5.0	40 "	2 "	"	Neg.	"
4/19/16	XVI	9	"	3-7 "	153.3	0.3-17.0	91 "	2 "	"	"	"
6/19/16	XX	16	"	3-7 "	88.8	0.3-10.0	98 "	3 "	"	"	"
6/22/16	XXI	17	"	3-7 "	135.8	0.3-13.0	111 "	1 "	"	"	"
8/9/16	XXIII	26	"	3-7 "	370.0	0.3-20.0	173 "	1 "	"	"	"
10/11/16	XXIV	30	"	3 "	98.8	0.3-13.0	92 "	10 "	"	Albuminuria, casts	"
10/13/16	XXV	31	"	3-7 "	1.8	0.3-1.0	9 "	1 "	"	Neg.	"
10/23/16	XXVI	33	"	3 "	4.6	0.3-2.0	47 "	6 "	"	"	"
11/3/16	XXVIII	36	"	3 "	153.8	0.3-15.0	72 "	1 "	"	"	"
12/30/16	XXIX	37	"	3 "	3.3	0.3-1.5	13 "	1 "	"	"	"
1/22/17	XXX	44	"	3 "	3.3	0.3-1.5	13 "	1 "	"	"	"
3/19/17	XXXV	51	"	3 "	224.3	0.3-18.0	81 "	1 "	"	Albuminuria	"
3/19/17	XXXVI	52	"	3 "	30.3	0.3-7.0	33 "	2 "	"	Neg.	"
3/20/17	XXXVII	53	"	3 "	102.0	0.3-12.0	53 "	1 "	"	"	"
3/19/17	XXXVIII	54	"	3 "	144.3	0.3-15.0	67 "	4 "	"	Albuminuria	"
3/20/17	XXXIX	55	"	3 "	12.3	0.3-4.0	25 "	3 "	"	"	"
3/20/17	XL	56	"	3 "	323.3	0.3-25.0	108 "	2 "	"	"	"
3/24/17	XLI	57	"	3 "	23.3	0.3-6.0	28 "	1 "	"	Neg.	"
3/24/17	XLII	58	"	3 "	57.3	0.3-10.0	42 "	1 "	"	"	"
3/31/17	XLIII	59	"	3 "	28.5	0.5-7.0	32 "	8 "	"	"	"
5/1/17	XLIV	60	"	3 "	158.5	0.5-20.0	66 "	2 "	"	"	"
5/1/17	XLV	61	"	3 "	148.5	0.5-18.0	66 "	2 "	"	"	"
5/5/17	XLVIII	64	"	3 "	15.5	0.5-5.0	18 "	1 "	"	Slight albuminuria	"
5/5/17	L	66	"	3 "	10.5	0.5-4.0	15 "	2 "	"	Neg.	"
5/5/17	LI	67	"	3 "	21.8	0.3-6.0	29 "	2 "	"	"	"

TABLE IV—RABBIT

Date	Experiment No.	Animal No.	Staphylococcus aureus	Age of culture	No. of c.c. injected	Dose (in c.c.)	Length of life after first injection	Length of life after last injection	Method of injection	Urinary changes	Amyloid
5/4/16	XVII	12	Killed	48 hours	99.3	0.3-13.0	77 days	2 days	Intravenously	Albuminuria	Neg.
5/26/16	XVIII	13	"	48 "	441.8	0.3-15.0	249 "	1 "	"	Neg.	"
5/26/16	XIX	14	"	48 "	1.8	0.3-1.0	9 "	2 "	"	"	"
8/4/16	XXII	20	"	48 "	158.0	0.5-14.0	167 "	7 "	"	"	"
10/27/16	XXVII	35	"	48 "	37.0	0.3-8.0	66 "	1 "	"	"	"
1/31/17	XXXI	45	"	48 "	11.3	0.5-3.0	32 "	1 "	"	"	"
1/31/17	XXXII	46	"	48 "	20.3	0.3-5.0	41 "	1 "	"	"	"
3/16/17	XXXIII	47	"	48 "	131.3	0.3-15.0	73 "	6 "	"	Albuminuria	"
3/16/17	XXXIV	48	"	48 "	156.3	0.3-16.0	77 "	3 "	"	"	"
5/5/17	XLVI	62	"	48 "	10.8	0.3-4.0	23 "	6 "	"	Neg.	"
5/5/17	XLVII	63	"	48 "	38.8	0.3-8.0	41 "	3 "	"	"	"
5/5/17	XLIX	64	"	48 "	3.8	0.3-2.0	12 "	3 "	"	"	"

during the early stages of the experiment and only later began to show albuminuria and casts.

Other authors, such as Neisser and Wechsberg, Stoddard and Woods, and Major, have also found lesions in the kidney after the injection of cultures or filtrates from bouillon cultures of *Staphylococcus aureus*. Although Jackson and Le Count found spontaneous renal lesions in 11 out of 50 rabbits, Major, in examining a large number of normal rabbits, found that none of them showed such extensive changes as in those subjected to the staphylococcus injections.

No conclusions concerning the chief point of this problem can be reached from the present series of experiments, since no amyloid degeneration was produced, but it is at least shown that the artificial production of amyloid is very difficult and inconstant, even when methods are employed which have sometimes been successful. Renal lesions are produced, it is true, but it appears that the factor responsible for the production of amyloid is as yet unrecognized.

In conclusion, it gives me great pleasure to extend my thanks to Drs. Welch and Winternitz for their many helpful suggestions and directions.

I also wish to thank Dr. Bayne-Jones for the supply of bacteria, and Dr. Dayton for help in the arrangement of instruments.

Moreover, I take pleasure in expressing to Dr. Janeway and Dr. Hooker my sincere appreciation of the facilities afforded by them and directions as to examination of blood pressure, and also to Dr. Garrison in the Surgeon General's Office in Washington for his kindness in translating some foreign journals for me.

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## ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin.  
Prepared by the Authors.

THE USE OF FREE GRAFTS OF WHOLE-THICKNESS SKIN FOR THE RELIEF OF CONTRACTURES<sup>1</sup>

By JOHN STAIGE DAVIS, M. D., F. A. C. S., Baltimore, Md.

(Abstract from Surg., Gynec. and Obst., 1917)

The contractures considered are those following burns, injuries and infections, in which the skin and often the subcutaneous tissue has been completely destroyed. Many methods have been suggested and tried for their relief.

The use of pedunculated flaps is especially valuable when a pad of fat is required in addition to the whole thickness of the skin, but this method can be used only in selected cases. The small thin grafts of Reverdin and the larger grafts of Ollier-Thiersch are not, as a rule, effective, especially in exposed positions, both on account of the danger of recontraction under the graft and also because of the instability of the result. The large graft of whole thickness furnishes a solution of the problem which I have found most satisfactory.

TECHNIC. *Preparation of the Area to Receive the Graft.*—

All of the scar tissue should be excised, if this can be done with safety, but in many instances the entire part is covered with scar and in these only the contracture should be entirely excised, while the movable scar tissue beyond should be utilized.

It is of the utmost importance that the raw surface on which the graft is placed be perfectly dry. If the graft is placed on an oozing wound, the chances are that a blood clot will form beneath it, and this will often seriously interfere with its new blood supply.

Whole-thickness grafts may also be successfully placed on undisturbed healthy granulations which are level with the skin edges.

*Cutting and Placing the Graft.*—Mark out lightly with a scalpel on the skin an elongated ellipse, bearing in mind that the edges of the wound caused by removal of the graft should be approximated with but little tension. Remove the skin with the underlying fat down to the fascia or aponeurosis covering the muscle. As soon as the scalpel has penetrated the subcu-

<sup>1</sup> Read before the Southern Surgical Association, December, 1916.



taneous fat the skin immediately shrinks about two-thirds of its original size transversely, and a little less in its length, and this shrinkage must be planned for. Wrap the graft in dry gauze until the wound from which it is taken is sutured and dressed. Then trim off all the fat from the graft with curved scissors. Perforate the graft in several places to allow the escape of any blood or secretions which may collect. Fit the graft into the defect, either in one piece or in several pieces, depending on the shape of the wound. If one piece can be used, it is advisable to secure it without tension by four cardinal sutures. In some instances a continuous horse-hair suture is used to fill in between the cardinal sutures, and in others a few interrupted sutures. Occasionally no sutures are used, as the graft adheres closely to the dry wound, but in these instances the graft should be secured by means of rubberized mesh. A slight even pressure should be exerted on the graft to hold it firmly against its base, but too much pressure should be avoided, as it interferes with the vitality of the graft. The graft should be handled as little as possible.

I consider it essential that the wound from which the graft is taken should be closed at once. It is better to have the graft too large than too small. It is desirable to fill a defect with a single piece of skin, as there are fewer resulting scars, but this is often impossible.

*Dressings.*—Silver foil; dry gauze; moist salt gauze which is kept wet, or which is allowed to dry out, are all excellent dressings. Another dressing which I have found useful is a flexible paraffin mixture used by Carrel for another purpose.

In children under 10 years of age, I find that it is always advisable to put the part up in a plaster cast. If there are no contraindications I do not disturb this cast for at least three weeks.

*Anesthetic.*—A general anesthetic is usually necessary in order to remove the contracture and to prepare the wound for the graft, but whole-thickness grafts may be easily secured and successfully transplanted with the use of a local anesthetic.

*Iso- and Zöo-Grafts.*—There is much difference of opinion as to the advisability of utilizing iso-grafts, but I feel convinced that, when it is not possible to utilize auto-grafts, iso-grafts are well worth trying.

Many successes have been reported following the use of zöo-grafts. My own experience is that these grafts take readily and receive their blood supply as promptly as ordinary grafts, but eventually they disappear.

*Remarks.* Contractures are more likely to follow in these cases which heal by granulation. They are much less likely to occur in cases where the healing is properly assisted by skin grafting, or by plastic operation.

When contracture of an eyelid is dealt with, it is seldom possible to remove all the scar, but all tension can be relieved. It is advisable to markedly over-correct in relieving these deformities, as the subsequent shrinkage of the scar, and wrinkling and folding of the skin in this situation have to be taken into consideration.

A graft of whole thickness may be placed successfully in the midst of movable scar tissue, and accomplish its purpose.

Gentle massage of the grafted area should be started several weeks after operation, and the manipulation gradually increased until the graft moves freely with the surrounding skin.

The operative procedure in securing thick grafts is undoubtedly much greater than in securing thin grafts, and occasionally the after-care is difficult and tedious, but the healing following a successful whole-thickness graft is as stable, firm and pliable as the original skin.

Contractures causing complete or partial loss of function, and accompanied by hideous and crippling deformities, may be relieved by the use of free grafts of whole-thickness skin, and the part restored to its former usefulness.

#### A RACK FOR FACILITATING THE HANDLING OF SMALL DEEP SKIN GRAFTS

By JOHN STAIGE DAVIS, M. D., F. A. C. S., Baltimore, Md.

(Published in the Jour. Amer. Med. Assoc., 1917)

The appliance is used for facilitating the handling of small deep skin grafts. When two or more men are working on a large wound, the grafts are often cut faster than they can be applied, and there may be no convenient way of stacking the artery clamps holding needles and grafts. In consequence an instrument is often upset or slips; the graft is brushed off, and is lost or else much time is wasted in trying to pick it up. In order to eliminate this inconvenience, I have devised a slotted metal rack to hold the clamps.

The rack is made of 18-gauge sheet copper, which is bent so that the end view shows the form of a trapezium. The longest side of this figure is used as the base, and to facilitate cleansing is open, except for three strips which are necessary to brace it. The 12 slots are made on the side opposite the base and each is wide enough to admit the ordinary Halsted artery clamp.

The measurements of the rack are as follows: Base, 9 cm. long. Surface carrying slots, 6.5 cm. long. Sides, 5.5 and 6.5 cm. long. The full length of the rack is 15 cm.

The rack can be used with great comfort when one man is cutting and also placing the grafts. The 12 slots are filled and the rack is then moved close to the wound to be grafted, and all the grafts are then applied, the maneuver being repeated as often as necessary. It can readily be seen that an enormous amount of labor is thus saved, since without this frame each graft would have to be placed on the wound as it was cut.

If more space is desired, a longer rack or two racks could be used.

When a large wound is being grafted with small deep grafts, the method of procedure is as follows: The rack, with its highest side towards the operator, is placed in a convenient position. Then, as the grafts are cut, the clamps are dropped into the slots, and when the cutting is faster than the placing, the clamps are moved along progressively towards the placer, by the nurse, so that those grafts first cut will be applied first.

THE INTERRELATION OF THE SURVIVING HEART AND  
PANCREAS OF THE DOG IN SUGAR METABOLISM—  
SECOND PAPER

By ADMONT H. CLARK

(From the Department of Pathology, Johns Hopkins Hospital and University)

(To appear in full in the Journal of Experimental Medicine)

1. When a sterile, oxygenated Locke's solution, containing dextrose in physiological concentrations, is perfused aseptically through the pancreas of a dog, the optical rotation of the perfusate is diminished but there is no change in the reducing properties. An osazone with a lower melting point than glucosazone can be obtained from the perfusate. Hydrolysis of the perfusate tends not only to restore the original rotation but also yields an osazone with the same melting point as glucosazone. These changes take place also if dextrose is added to a pancreatic perfusate and the mixture subsequently allowed to incubate. An extract of a portion of the same pancreas does not bring about these changes. With a Locke's solution containing levulose, however, neither the optical rotation nor the reducing properties are altered by perfusion through the pancreas. A Locke's solution which contains both dextrose and levulose, and is therefore balanced in its rotation between the two sugars, when perfused through a pancreas, shows a displacement of the balance to the left. The reducing properties of such a perfusate remain unchanged and hydrolysis, again, increases the positive rotation. The spleen perfused with the same balanced solution shows neither a shift in the optical rotation nor a diminished reducing power. The preceding facts can be accounted for only by a specific action of the pancreas on dextrose.

2. When a living dog's heart is perfused aseptically with physiological concentrations of dextrose or levulose in oxygenated Locke's solutions and the final perfusates hydrolyzed, there is no increase on hydrolysis in the amount of reduction, nor any significant change in the optical rotation. A similar negative effect is obtained when a pancreatic perfusate containing levulose is circulated through an actively beating heart. It is only when a pancreatic perfusate containing dextrose is fed to a heart that a perfusate is obtained, which on hydrolysis gives a definite increase both in reduction and in optical rotation. The change in rotation is additional to the preliminary effect of the pancreas, and the increased reduction on hydrolysis is evidence that the change produced by a pancreas alone is qualitatively different from that produced by the combined action of the heart and pancreas.

When a balanced Locke's solution of dextrose and levulose is perfused through a heart alone there is a definite utilization of sugar as shown by the diminished reduction, but the optical rotation is only slightly shifted, if at all, to the left. This shows that both sugars have been used. Hydrolysis of the perfusate, also, gives no material change in its reducing properties or rotation. Such a balanced Locke's solution, however, under the combined action of the pancreas and heart, after correction for the preliminary change of rotation due to the pancreas, gives a striking and marked displacement of the rota-

tion to the left, indicating that the selective utilization of dextrose has been greatly accelerated. Hydrolysis, also, gives a partial restoration of the original balance in rotation.

Further evidence for the specific relation which the combined pancreas and heart have for dextrose is obtained from the action of bromine on Locke's solutions containing both dextrose and levulose, which have been perfused through the heart alone and through both the pancreas and the heart. If the dextrose is removed from the perfusate by destructive action of bromine, the heart taken alone is found to have used a considerable amount of levulose, whereas the heart and pancreas together select the dextrose, leaving the levulose fraction practically untouched.

Finally, the heart, perfused with dextrose, does not lower the melting point of osazone obtained from the final perfusate, whereas an osazone from a pancreas perfusate or heart pancreas perfusate has a distinctly lowered melting point. After hydrolysis of the perfusates, however, the melting points of the osazones correspond to that of glucosazone.

The explanation which at present seems to be most consistent with these facts and with those brought out in my previous work would seem to be as follows: The pancreas supplies to a perfusate some enzyme or enzymes which have a specific action on dextrose as compared to levulose, changing a certain portion of the dextrose to a simple form of polysaccharide. This polysaccharide has both a lower optical rotation, and a lower melting point of its osazone than dextrose. I should regard this sugar complex as either relatively unstable, being hydrolyzed during the reduction determination, or as having the same reducing properties as dextrose. When, however, the pancreatic perfusate is circulated through a living heart the optical rotation not only continues to diminish but a new change occurs. The reducing properties of the perfusate are now altered. Thus the effect of the heart seems to be the production of a change additional to that caused by the pancreas. The most probable explanation would seem to be a further polymerization of the sugar in the presence of the living heart to a more stable form with a diminished power of reduction.

From the experiments here reported, it cannot be determined whether the specific sensitization of the heart for dextrose is dependent merely upon the preliminary change in the sugar produced by the pancreas. It seems quite probable that the action of the pancreatic enzyme does not cease with a simple polymerization but that it initiates a number of changes, the subsequent steps of which are dependent upon the interrelation of the enzyme with the living heart. So far as the heart alone is concerned, there is a similarity in its action to that of an eviscerated diabetic animal as described by Macleod and Pearce. In both there is a certain apparent utilization of dextrose, but for the isolated heart, at least, this utilization is non-specific, for it occurs almost equally well with levulose. In both, however, there is a certain fundamental incompleteness in the power to utilize sugar. With the heart, by supplying a pancreatic perfusate, a highly specific relation is established between it and the circulating dextrose, which not only causes an immediate and rapid utilization of dextrose, but

also brings about a certain condensation of dextrose which can be initiated by the pancreas alone.

This specific interrelation of the pancreas and heart to dextrose suggests that in normal sugar metabolism this pancreatic enzyme, or enzymes, may be necessary; that certain stages of synthesis and polymerization may be of importance as intermediate steps in carbohydrate utilization; and that when there is an insufficiency of the pancreatic function, though the body tissues are supplied with an abundance of dextrose which can be burned to a certain extent, yet the essential steps, by which dextrose is prepared for normal utilization, cannot take place.

#### A NEW METHOD FOR MAKING WASSERMANN ANTIGENS FROM NORMAL HEART TISSUE

By CHARLES A. NEYMANN and LESLIE T. GAGE

(Abstract from *Journal of Immunology*, October, 1917)

After describing the methods in use for the production and titration of Wassermann antigens, and giving an account of their investigations of the various lipoids of beef's heart which were prepared according to Erlandsen's method, the authors say:

"The diaminomonophosphatides which comprise over half by weight of the secondary alcohol soluble lipoids, have an extremely high antigenic value as well as a low anticomplementary and hemolytic titre. Therefore it is with this group that we are primarily concerned in making a good Wassermann antigen.

"Considering these facts and using the knowledge gained we propose the following methods for making antigens:

"Take a normal beef heart and remove all the endo- and pericardium, larger blood vessels and fat. Grind the heart muscle very fine and spread it in a thin layer on glass plates. Dry by means of an electric fan for 24 hours, turning the layer of tissue after 12 hours. A parchment-like dry sheet of tissue results. Break this up and grind it again, thus producing a fine dry powder. Put this in bags and dry in an incubator at 37° C. for several days. Extract with ether in a Soxhlet apparatus for 12 hours, or in an ordinary wide-mouthed bottle at room temperature five or six times until the supernatant ether is no longer colored yellow. The latter procedure takes from 8 to 10 days. The ether should cover the muscle powder to a depth of from 2 to 3 inches. Dry the powder by spreading it out on a sheet of paper for several hours. Now extract the powder with absolute or 95 per cent alcohol for 10 days. The alcohol should cover the powder to a depth of half an inch and it will gradually assume a light yellow color. Titrate the antigen thus obtained. Extract the powder a second time with alcohol for 14 days. Titrate this antigen.

"Both extracts will prove to be good plain extracts. Sometimes the second will be better than the first, for the diaminomonophosphatides seem to go into solution after some of the other groups of the secondary alcohol extract have been dissolved out.

"In order to produce an acetone insoluble extract the plain extracts are united, evaporated to dryness at room temperature by means of a fan and treated with an excess of ether. The

ether-soluble portion is filtered off, allowed to evaporate, treated with an excess of acetone and the sticky brown residue is finally dissolved in a minimum quantity of absolute alcohol. The solution is then filtered and again titrated.

"This preparation consists almost entirely of diaminomonophosphatides and with 10 hearts prepared in succession has, each time given an antigen which bound at least 1 to 1600, and showed a low anticomplementary titre and no hemolytic properties.

"A cholesterinized antigen can be made by adding 0.2 gm. of cholesterin to 100 c. c. of the plain extract or of the acetone-insoluble preparation. The cholesterin will dissolve very readily in either of these phosphatide solutions, much more readily than in the same amount of absolute alcohol. After the addition of cholesterin the antigen is again titrated.

"These antigens have been in use in our laboratory for the past six months. They have proven reliable in every way and have solved the problem of finding a certain and definite method of obtaining a reliable, fairly equal, and powerful product. Though these antigens pick up weaker positives than our former preparations they have never given false positives."

#### A NEW PATHOGENIC SPOROTRICHUM. FOUND IN A CASE OF ACUTE ARTHRITIS OF THE KNEE, FOLLOWING INJURY

By S. B. WOLBACH, M. D., W. R. SISSON, M. D., and F. C. MEIER, Ph. D.

(From the Department of Pediatrics, The Johns Hopkins Hospital)

Instances of infection with sporotricha following injury, in America, are of unusual interest in the consideration of presumably free living pathogenic fungi. The study of the culture from the case here presented has revealed a new variety of sporotrichum for which the name *Sporotrichum councilmanii* is proposed.

The culture of this organism was obtained from the knee-joint of a boy of 10 years. This patient received a puncture wound of the right knee from the nail of an ash barrel. Following the injury there took place within 12 days, signs and symptoms of an acute arthritis which could not be explained by the common causes of this condition. The swollen knee was aspirated repeatedly. Large quantities of sanguineous muco-purulent material were recovered. This showed microscopically numerous pus cells without the presence of demonstrable organisms. Cultures showed the presence of a fungus growth. Using a suspension of this fungus as an antigen, the patient's serum showed complete fixation in various dilutions. Similarly, agglutination tests with the patient's serum were positive up to dilutions of 1-100. The patient was observed at the hospital for six months. The condition of the knee was unimproved after the usual forms of treatment. X-ray examination showed no bony changes. Complete fixation of the joint took place. Shortly before his discharge from the hospital all signs of acute infection disappeared. A study of the pathogenicity of the fungus isolated from the patient's joint was made by injecting guinea-pigs and rabbits intraperitoneally,



by injecting rats intravenously and rabbits intraarticularly. By the first method the organism was found to be of low pathogenicity, causing a granulomatous lesion of the peritoneal lymph nodes. These animals did not succumb to the injection. The intravenously injected rats showed multiple focal abscesses in the brain, thoracic and abdominal organs. After the injection of the fungus into the knee-joint of the rabbit, an acute arthritis was produced which simulated in every way that of the patient.

Microscopically, the lesions resembled those of actinomycosis and the organisms of cutaneous blastomycosis and coccidioides granuloma. The first reaction is the collection of polymorphonuclear leucocytes and endothelial cells about the organisms. Giant-cell formation and the taking up of the spores by endothelial cells and giant cells occur. The mycelial fragments always seem to disappear soon after injection. At the periphery of the lesions fibroidblast proliferation becomes active. The lesion progresses only following the germination of the spores with the production of branching filaments radially arranged. Late lesions consist of fibrous nodules containing foci of soft yellow necrotic material. The organism was early identified as a sporotrichum. It grows readily on all ordinary

culture media at room temperature. The gross cultural appearance differs from most pathogenic sporotricha in that it produces a profuse areal growth of white cotton-like hyphae. This has not been seen with the other sporotricha. Microscopically the hyphae and spores are distinctly larger than those of other sporotricha. Furthermore, this organism does not produce lateral spores or conidia from vegetative hyphae. Like other sporotricha there is great variation both in regard to the form of the growth and pigment production. Comparison of this organism with *Sporotrichum schenkii* and *Sporotrichum beurmannii*; and with cultures from a case of sporotrichosis described by Page, Frothingham and Paige, shows striking differences, especially the gross cultural appearances. Comparison also with descriptions of other isolated pathogenic sporotricha warrants us in considering this an hitherto undescribed form. It resembles most closely *Sporotrichum jeanselmei* in gross cultural characteristics, in pleomorphism and in luxuriance of growth upon simple media. It shows, however, a much greater tendency to areal growth of the filaments. Microscopically, it is different from all species in the absence of lateral clusters of spores. The form of the organism in lesions, namely, that of branching hyphae, is unusual.

## TITLES OF PAPERS APPEARING DURING THE YEAR, ELSEWHERE THAN IN THE BULLETIN, BY PRESENT AND FORMER MEMBERS OF THE HOSPITAL AND MEDICAL SCHOOL STAFF

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# BULLETIN

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## URETERO-VENOUS ANASTOMOSIS WITH OBSERVATIONS ON EXPERIMENTAL HYDRONEPHROSIS AND THE BLOOD NITROGEN

By MONT R. REID,

*Instructor in Surgery*

(From the Hunterian Laboratory of The Johns Hopkins University)

In the course of some experimental work on the blood-vessels of dogs in which arterio-venous fistulae were made in various situations, it occurred to me to test the effect of anastomosing the ureters with the venous system. I had particularly in mind the possibility that the kidneys might increase or decrease the toxicity of substances which they eliminate from the blood. In addition to this point, these experiments have permitted me to make some interesting observations on the mechanism of the production of hydronephrosis.

In connection with various problems a great deal of contradictory experimental work has been done on the kidneys and ureters of animals. Brown Séquard<sup>1</sup> thought that the kidneys possessed an internal secretion of great importance and even regarded uræmia as due more to the absence of it than to the retention of toxic substances. To a certain extent his idea has been supported by the work of Bradford<sup>2</sup> and others, but by Pearce,<sup>3</sup> who has removed as much as three-quarters of the total kidney substance without evident impairment to the body function, the presence of an internal secretion has been doubted. By many investigators<sup>4,5</sup> the most marked hydronephrosis has been produced by only partial obstruction of the ureter, whereas others<sup>6</sup> have noted that complete has been as

effectual as partial obstruction. Some<sup>7</sup> have observed the dilation in hydronephrosis to begin near the pelvis of the kidney and proceed toward the point of obstruction in the ureter, others<sup>8</sup> that the reverse occurs. The cause of the ureteral pressure in obstruction in the ureter and the effect of the pressure on the kidney secretion have received different interpretations from the various investigators.<sup>7</sup> Similarly, in many other problems regarding the kidney and ureter, interesting differences of opinion exist. Most work has had to do with a disturbance of the kidney function or the natural outlet for its secretion. And these experiments have only slight bearing on the big problems of chemistry involved in the study of diseased kidneys and experimentally impaired renal function, or with the transplantation of the ureters elsewhere than into the blood-stream.

Practically all investigators<sup>2,4,5</sup> are agreed that dogs usually die in from three to five days after a double nephrectomy or the ligation of both ureters, and that the ligation of one ureter is compatible with life for an indefinite period. Various transplantations of the kidney and ureter have been made, but, so far as I know, in dogs the effect on life of single and double uretero-venous anastomosis has not hitherto been attempted.



The chemical studies in these experiments were made in the laboratory of the chemical division of the medical clinic. For these data and for valuable suggestions I am greatly indebted to Dr. H. O. Mosenthal.

#### TECHNIQUE

The method of anastomosis is shown in the accompanying illustrations (Vide Figs. 1, 2). In all the experiments the right ureter was introduced into the vena cava; when a double

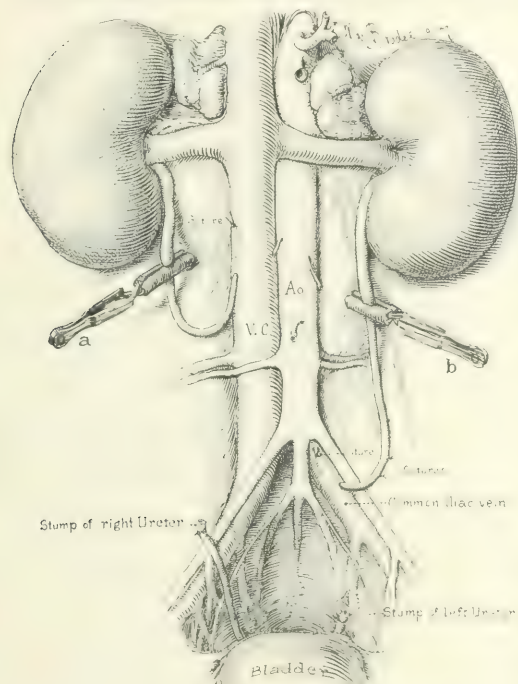


FIG. 1.—With clamps *a* and *b* removed, the uretero-venous anastomosis is complete. V.C.=vena cava. Ao=Aorta.

anastomosis was made, the left ureter, at a later period, was introduced into the left common iliac vein. The abdomen was entered either through the rectus muscle or through a transverse incision. The ureter was blocked at a point about 6 cm. from the pelvis of the kidney, by means of a Crile clamp, and considerable pressure was allowed to develop in the ureter by the time the anastomosis was completed. A segment of vein, 2.5 cm. long, was carefully freed and its blood-stream interrupted by temporary ligatures or clamps. Then an opening in the vein which the ureter would just fill was made, and through it the segment of the vein was washed free of blood with normal salt solution and alcohol. The ureter was then divided obliquely, at such a distance from the bladder that it could be gently curved without kinking, and introduced into the vein in the direction of the blood-stream. Central to the opening for the ureter a half-curved needle, threaded with 00000 silk was introduced into the lumen of the vein and brought out

through the opening. The pointed end of the ureter was then caught in the suture and the needle passed back through the foramen into the vein and brought through the vein wall close to where it was first introduced. After this mattress suture had been tied, the ureter was pulled into the vein lumen and sutured to its inner wall. The clamps were then removed and the blood allowed to resume its course. Rarely was it necessary to close the slit in the vein with a suture in order to prevent bleeding. Occasionally the adventitia of the ureter at the curve was sutured to the parietal peritoneum in order to prevent kinking of the ureter. All bleeding vessels were tied and all wounds closed with silk.

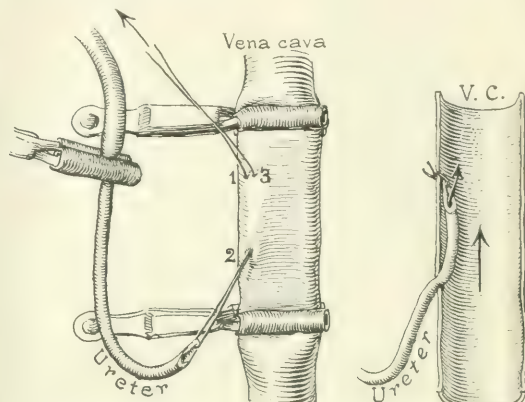


FIG. 2.—Numbers 1, 2 and 3 show the order in which the suture is made. To the right the ureter is shown sutured to the inner wall of the vein.

#### EXPERIMENTS

The following are the complete protocols of the experiments with the exception of the chemical findings which are detailed further on:

##### Dog 1

May 1, 1917. Through a right rectus incision the right ureter is anastomosed into the vena cava. Before this anastomosis is made, blood is taken from the vena cava for chemical analysis.

May 2. The dog is in good condition; 10 c. c. of blood are taken from the jugular vein.

May 4. Except possibly for an increased thirst for water nothing abnormal is noted. The wound appears healthy and shows practically no reaction.

May 14. The wound has healed *per primam*. The general appearance is that of a normal animal. The appetite is good.

June 27. The condition of the animal seems to be perfect. There has been no apparent loss of weight. It has been nearly two months since the first uretero-venous anastomosis was made.

*Second Operation.*—Through a low left rectus incision the left ureter is anastomosed into the left common iliac vein. The right kidney on palpation seems a little large and somewhat cystic.

June 29. The dog is drowsy, but is apparently in fair condition. He is taking food and water very well.

June 30. The drowsiness is somewhat more marked. The animal still walks about and eats food.

July 4. For the past two days the dog has not eaten food and has been very drowsy. Death occurred this morning.

**Autopsy.**—There is a slight superficial infection of the wound but no peritonitis is present. The entire right ureter is markedly dilated and tortuous. The left ureter is dilated for a distance of about 2 cm. above the point of the anastomosis. The vein at both points of anastomosis is patent, and no clot formation is present. The intravenous part of the right ureter is dilated; the end of the ureter sticks close to the vein wall and is patent. Light pressure on the kidney or ureter forces urine into the vena cava. The end of the left ureter is open and fluid injected into the ureter flows readily into the vein.

The right kidney shows a very marked grade of hydronephrosis without any sign of infection. The pelvis of the kidney contains what is apparently clear, normal urine. The somewhat thinned cortex shows a normal gross picture. The left kidney is slightly swollen and injected, but there is no dilation of the pelvis. A little urine, which appears to be normal, is present in the pelvis. The capsule of both kidneys strips readily. In neither ureters nor kidneys is there any blood.

**Weights:**

Dog .....	13.5 kilos
Heart .....	140 grams
Right kidney .....	85 "
Left kidney .....	75 "

**Histology of Kidneys.**—Right kidney: The glomeruli appear to be normal. The collecting tubules stand out prominently and appear to be somewhat dilated. They contain no albuminous material nor red blood cells. The epithelium of the convoluted tubules is practically normal. The nuclei stain well. There is no fibrous tissue increase. There is no polymorphonuclear nor round-cell infiltration.

Left kidney: The only possible abnormality suggested in the sections is an occasional slight swelling of the tubular epithelium and the presence of a small amount of albuminous material in the tubules.

**Dog 2**

May 2, 1917. Through a transverse incision the right ureter is anastomosed into the vena cava.

May 7. The condition of the dog is excellent. She takes food well and shows no evidence of a toxic condition.

May 14. The wound has healed *per primam*. Condition is excellent. Animal takes food and water well.

June 27. The dog is in perfect health.

**Second Operation.**—Through a low left rectus incision the left uretero-venous anastomosis is made.

June 29. The dog is drowsy, but walks about and eats perfectly well. There is no unusual sweating. Edema is not apparent.

June 30. The condition is about the same as yesterday.

July 5. For the past two days the dog has practically not eaten and has been very toxic. It died this afternoon.

**Autopsy.**—The animal is still warm. Both wounds are perfectly healed and there is no infection.

An organizing thrombus occludes the vena cava from the point of the first anastomosis down for a distance of 3 cm. Below this a fresh ante-mortem clot extends down to the bifurcation of the vein and into the left iliac to the point of the last anastomosis. This thrombus does not occlude the vessel.

The right ureteral orifice is pervious and empties into the vein just above the point of occlusion by the thrombus. The entire right ureter is dilated and tortuous. Pressure on this or on the pelvis of the kidney causes urine to pass into the vein.

The left ureteral orifice is open and water injected into the ureter passes readily into the vein. This ureter for 3 or 4 cm. above the anastomosis is dilated.

There is a marked hydronephrosis of the right kidney which contains apparently normal urine.

The left kidney, except for slight edema and injection, appears to be normal.

**Weights:**

Dog .....	13.7 kilos
Heart .....	150 grams
Right kidney .....	75 "
Left kidney .....	80 "

**Histological Examination.**—Right kidney: Section shows a moderate dilation of the tubules, a moderate degree of swelling of the convoluted tubules and occasionally a somewhat atrophied glomerulus. No hemorrhage, no polymorphonuclear nor round-cell infiltration. The nuclei stain well. No thickening of the blood vessels is apparent.

Left kidney: The only deviation from the normal suggested in the section is a slight swelling of the tubular epithelium.

**Dog 3**

May 3, 1917. Through a transverse incision the right uretero-venous anastomosis is made.

May 7. The dog is bright, playful, and eats.

May 14. The wound has healed *per primam*. The animal seems to be in perfect health.

June 29. The single anastomosis has apparently not affected the health of the dog.

**Second Operation.**—Through a low left rectus incision the left uretero-venous anastomosis is made. To palpation the right kidney is large and soft.

June 30. The dog takes food and water. Seems to be a little drowsy.

July 6. The drowsiness increased; the appetite for food and water disappeared, and the dog died this morning.

**Autopsy.**—The wounds are clean. There is a marked hydronephrosis of the right kidney. The pelvis is distended with a cloudy urine. It is injected and fibrin is deposited in the calices of the kidney. The capsule of the kidney strips readily. The cortical striations are not very regular. The right ureter is markedly dilated and tortuous. The end of the implanted ureter is not pervious, but is grown over by a smooth intima. The intravenous portion of the ureter forms a little pouch projecting into the lumen. Pressure on the pelvis of the kidney or the ureter does not force fluid into the vein.

The left ureter is patent and water injected into it passes readily into the vein. The ureter is dilated near the point of the anastomosis. The left kidney seems to be practically normal except for a possible slight dilation of the pelvis.

**Weights:**

Dog .....	12 kilos
Heart .....	150 grams
Right kidney .....	80 "
Left kidney .....	75 "

**Histological Examination.**—Right kidney. The section shows an extreme grade of chronic diffuse nephritis characterized by an extensive proliferation of connective tissue with corresponding compression atrophy, and obliteration of the tubular elements. The glomeruli show thickened capsules but no adhesions between the capsules and tufts, and obliterative changes in the vessels. Isolated areas of mononuclear and polymorphonuclear infiltrations are found, especially in the region of the pelvis, but these are not a prominent feature.

Left kidney: The tubular epithelium is swollen and in some areas there is a suggestion of early degenerative changes. No infection. No fibrosis.

## Dog, 4

May 3, 1917. Through a transverse incision the right ureter is anastomosed into the vena cava.

May 7. The dog does not appear to be drowsy. He takes food and water well.

May 14. The wound has healed *per primam*. The condition of animal is excellent.

June 29. The animal seems to be in as good condition as before the anastomosis was made.

*Second Operation.*—The left uretero-venous anastomosis is made.

June 30. The dog seems to be a little toxic but is otherwise in fair condition.

July 3. Death rather unexpectedly about noon to-day. The dog ate his breakfast and drank some water.

*Autopsy.*—The vein is normal in appearance. The mouth of the right ureter is easily seen. Pressure on the ureter or hydronephrotic kidney causes urine to empty into the vein. The pelvis of the right kidney contains urine which appears to be normal.

The left ureter is slightly dilated just above the point of the anastomosis. The anastomosis is also patent. The left kidney appears to be practically normal.

## Weights:

Dog .....	9.9 kilos
Heart .....	140 grams
Right kidney .....	50 "
Left kidney .....	70 "

*Histological Examination.*—Right kidney: The epithelium is low. The ducts are somewhat dilated. No evidence of infection.

Left kidney: There is some swelling of the tubular epithelium and at the pelvis a small area of leucocytic infiltration.

## Dog, 5

Nov. 7, 1916. Through a right rectus incision the right ureter is anastomosed into the vena cava.

Nov. 15. The wound healed *per primam* and the dog seemed to be in excellent condition yesterday. Death occurred during the night.

*Autopsy.*—The wound and peritoneal cavity are free of infection. Death was due to intestinal intussusception at the ileo-cecal valve.

The right kidney is markedly increased in size, weighing 122 grams. It has a reddish black appearance. The capsule is edematous and has a fibrous exudate over it. The right renal vessels are patent and normal. The capsule is stripped with difficulty, a rough red and white mottled surface being left. The pelvis is slightly dilated and contains a yellowish gelatinous material which extends in finger-like processes up into the calices. The pyramids are of a dark red color. The cortex is swollen and filled with hemorrhages. The striations are distinct. The glomeruli are easily seen.

The ureter is dilated and filled with a milky fluid. This passes readily into the vein through the pervious ureteral anastomosis. The left kidney and ureter appear to be normal.

*Histological Examination.*—The right kidney shows an extreme grade of acute nephritis; many clumps of bacteria are present.

The left kidney shows no infection and a normal structure.

## Cat 1

October 30, 1916. The right ureter is anastomosed into the vena cava.

Nov. 15. The cat seems to be perfectly normal.

Nov. 27. Death this morning.

*Autopsy.*—The body is well nourished. There is no edema and no ascites. The ureter is slightly dilated and the lymphatics along it are distended. The kidney except for a little dilation of its

pelvis appears to be normal. The ureteral opening is patent and fluid passes readily into the vein. No thrombus is present in the vein.

The left kidney is normal.

The right kidney weighs 13.5 grams, the left 15 grams. No cause for the death of the cat is found.

The hydronephrosis in these cases certainly resulted from a partial obstruction to the ureters. On the right side where the uretero-venous anastomosis had existed for two months the kidney in every animal showed a marked grade of hydronephrosis which involved the entire ureter and the pelvis of the kidney. On the left side, where the duration of the anas-

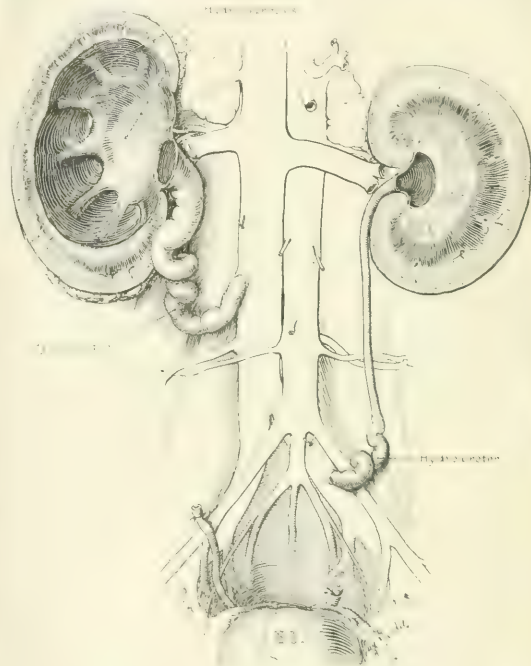


FIG. 3.—Hydroureter and hydronephrosis after uretero-venous anastomosis. The right dilation has developed in about two months, the left hydroureter in six or seven days. Note the ascending dilation on the left.

tomosis was from four to six days, the ureter for a short distance above the anastomosis was dilated, whereas the pelvis of the kidney was only slightly, if at all, dilated (Vide Figs. 3, 4 and 5).

It is impossible to say whether the dilation resulted from a partial narrowing of the ureteral orifice, which was not very evident, or to the resistance of the venous blood stream. It has been shown by Keith and Snowden<sup>7</sup> that hydronephrosis will develop when a ureteral pressure of from 10 to 30 c. c. of water is established by partial obstruction in the ureter. When the ureteral pressure does not exceed 50 c. c. of water, a polyuria with definite modification in the character of the urine excreted develops. The kidney secretion is not totally sup-



pressed until the enormous ureteral pressure of above 50 mm. of mercury is present. Bayliss and Starling<sup>9</sup> have found the normal vena cava pressure to vary between 2.5 and 7 mm. Hg. In the left femoral vein Burton-Opitz<sup>10</sup> found the pressure to be 5.39 mm. Hg. It has been shown<sup>11</sup> that the inferior vena cava pressure varies with the abdominal pressure so that both remain the same. The opening of the abdominal cavity certainly alters the venous pressure. It may be that the constant low pressure in the vena cava is sufficient to produce the hydronephrosis.

In Dog 3, who had a complete obstruction to the ureter, there was a high grade of hydronephrosis, associated with a marked fibrosis of the kidney substance. The belief, based erroneously on the work of Cohnheim<sup>12</sup> and other experi-

tion for a short distance above the anastomosis, but not in the renal end of the ureter and probably not in the pelvis.

*Chemical Studies.*—At frequent intervals, specimens of the blood were analyzed for their non-protein nitrogen and urea content. At autopsy the muscle was similarly studied, and a specimen of urine from the pelvis of each kidney was examined.

The total non-protein nitrogen was determined in the filtrate after precipitation with trichloroacetic acid, the method advocated by Greenwald<sup>13</sup> being used, except for the omission of the second precipitation with kaolin which was not found to be necessary. This procedure yields higher results than the use of alcohol as advocated by Folin and Denis<sup>14</sup> and in our experience has yielded data which are more nearly correct. The urea nitrogen was estimated according to Marshall.<sup>15</sup> The salt in

TABLE I

	Duration of Anastomosis	Fistula	Infection	Hydronephrosis	Weight of Kidney	Histology
<b>Dog 1</b>						
Rt. Kidney.....	63 days	Patent.	None.	Marked, involving pelvis and entire ureter.	85	Practically normal
Lt. Kidney.....	7 days	Patent.	None.	Present only in distal end of ureter.	75	Normal.
<b>Dog 2</b>						
Rt. Kidney.....	63 days	Patent.	None.	Involves pelvis and entire ureter.	75	Almost normal.
Lt. Kidney.....	9 days	Patent.	None.	Only the ureter and near anastomosis.	80	Normal.
<b>Dog 3</b>						
Rt. Kidney.....	63 days	Not Patent	Present.	Marked in pelvis and ureter. Pus present in urine.	80	Chronic diffuse nephritis, extensive. Moderate infection.
Lt. Kidney.....	7 days	Patent.	None.	Only in distal end of ureter.	75	Normal.
<b>Dog 4</b>						
Rt. Kidney.....	60 days	Patent.	None.	Marked in pelvis and ureter.	50	Epithelium low. Some dilation of ducts. Very little change from normal.
Lt. Kidney.....	4 days	Patent.	None.	Slightly dilated just above point of anastomosis.	70	Some swelling of tubular epithelium.
<b>Dog 5</b>						
Rt. Kidney.....	8 days	Patent	Present.	Ureter edematous and dilated; pelvis only slightly.	122	Extreme grade of acute nephritis.
Lt. Kidney.....	Not done	.....	.....	None.	.....	Normal.

menters,<sup>16</sup> is that atrophy of the kidneys follows complete ligation of the ureter. More recent investigators,<sup>17</sup> however, have obtained opposite results and report hydronephrosis following complete ligation of the ureter. The dilation in Dog 3 may have resulted before the ureter became totally occluded. Yet the extreme fibrosis here, as compared with the other hydronephrotic kidneys, may indicate that in complete ureteral ligation hydronephrosis does result, but that the kidney tissue rapidly becomes functionless and following the absorption of the urine in the pelvis, ultimately becomes contracted.

The results of our experiments are not confirmatory of the observations of those who believe that hydronephrosis begins near the pelvis of the kidney and descends toward the point of obstruction. In every instance the left ureter, which had been transplanted for only four to eight days, showed a dila-

tion for a short distance above the anastomosis, but not in the renal end of the ureter and probably not in the pelvis.

the urine was estimated by the Volhard method, and the nitrogen by the Kjeldahl process.

The upper limit of normal for the non-protein nitrogen of the blood under usual conditions of diet is about 40 mgm. per 100 c. c. and 15 mgm. for the urea nitrogen. This is true for human beings<sup>18</sup> and in our hands these figures have been equally applicable to dogs. After the first uretero-venous anastomosis the non-protein nitrogen of the blood is at the upper normal limit, exceeding it by a slight margin at times. It varied between 32 and 53 mgm. per 100 c. c. of blood for the first two weeks after operation. The blood urea nitrogen was also slightly increased during this period, varying between 13 and 26 mgm. At the end of two months the urea nitrogen varied between 11 and 18 mgm. Such a minimal increase may be regarded as due to the passage of the urine from the right

kidney into the veins and the inability of the left kidney alone to maintain an absolutely normal level of waste products in the blood during the first two weeks, and to the fact that subsequently it functionated more efficiently.

When the second uretero-venous fistula was complete, both the total non-protein nitrogen and the urea nitrogen of the blood rose at a very rapid rate, much as they do in dogs in

to the rate of urea accumulation in the blood and the length of life of the animal, are the same whether a complete nephrectomy is done or the kidneys remain intact and excrete urine into the blood stream. These experiments indicate that the waste products of the blood in their passage through the kidneys are not rendered less toxic, nor is the urea changed chemically. It may be that some of the other waste products

TABLE II.—ANALYSES OF THE BLOOD AND MUSCLE SHOWING THE EFFECT OF URETERO-VENOUS ANASTOMOSES  
(Values are given in milligrams per 100 c. c. of blood or 100 grams of muscle.)

## Dog 1

	Blood												Muscle	
	5/1	5/1	5/2	5/7	5/10	5/15	6/27	6/27	6/30	7/2	7/4	7/4	7/4	
Non-Protein Nitrogen .....	30	Anastomosis, right	42	33	36	46		Anastomosis, left			Autopsy	446	385	
Urea Nitrogen .....	8		24	23	18	22	13		138	238		305	255	

## Dog 2

		Blood										Muscle	
	5/2	5/3	5/7	5/10	5/15	6/27	6/27	6/29	7/2	7/5	7/5	7/5	
Non-Protein Nitrogen.....	Anastomosis, right	35	36	32	40		Anastomosis, left			Autopsy	523	460	
Urea Nitrogen.....		19	16	13	22	18		88	219		376	225	

## Dog 3

		Blood										Muscle	
		5/3	5/4	5/7	5/10	5/15	6/29	6/29	7/2	7/6	7/6	7/6	
Non-Protein Nitrogen.....	Anastomosis, right	42	33	36	39		Anastomosis, left		Autopsy	400	505		
Urea Nitrogen.....		24	15	15	23	11		167		308	218		

## Dog 4

		Blood										Muscle	
		5/3	5/4	5/7	5/10	5/15	6/29	6/29	7/2	7/4	7/4	7/4	
Non-Protein Nitrogen.....	Anastomosis, right	53	40	40	41		Anastomosis, left		Autopsy	349		468	
Urea Nitrogen.....		26	19	17	19	12		196		222		170	

which bilateral nephrectomy has been performed. Under the latter condition, in three experiments, the urea nitrogen in the blood at autopsy was found to vary between 232 and 321 mgm. These figures are comparable to those of 349 to 523 mgm. for the total non-protein nitrogen and 222 to 376 mgm. of urea nitrogen found in the present series. The duration of life in these three nephrectomized animals was from four to six days, a period of approximately the same length as after double uretero-venous anastomosis. It would appear therefore that the results obtained in both, in regard

of the blood, such as the creatin, amino-acids, etc., may be modified in passing through the kidneys; however, the data thus far obtained are not conclusive on this point and must be verified before any definite statement can be made regarding them.

The urine analyses as shown in Table II present some interesting features. Dogs 1 and 2, in which there was no infection of the pelvis of the kidney or the ureter, showed a very low concentration of salt and a comparatively high nitrogen content. This was true for both kidneys, for the side on which

there was a distinct hydronephrosis as the result of a uretero-venous anastomosis of two months' duration as well as for the kidney in which these conditions had only obtained for a few days. This would indicate that the urine secreted against pressure was not normal, but resembled that found in passive congestion of the kidneys.<sup>20</sup> A study of the urine in dogs when the hydronephrosis is produced by a ureteral pressure of 12 to 30 cm. of water shows a "polyuria, trace of albumin, diminished output of phenolsulphothalein and delayed excretion of lactose."<sup>21</sup> Under almost similar conditions Lépine and Porteret<sup>22</sup> and Schwartz<sup>23</sup> found that the concentration of urea nitrogen and sodium chloride was less than in normal urine,

TABLE III

Analyses of urine collected from the pelves of the kidneys at autopsy

	Amount of urine		Right		Left		Remarks
	Right	Left	NaCl%	N%	NaCl%	N%	
Dog 1	75 c.c.	About 5 c.c.	.06	1.09	.02	.97	Urea in pelvis of right
Dog 2	117 c.c.	About 5 c.c.	.04	1.20	.05	1.20	kidney (Dog 3). Ureter
Dog 3	33 c.c.	Small amount	.51	.48	....	....	not patent. Albumin, 6 grams per liter.

whereas Lindemann<sup>24</sup> observed that the sodium chloride remained unchanged. In human beings the character of the urine varies markedly with the degree of hydronephrosis and its cause. It may be normal;<sup>25</sup> the urea and sodium chloride content may be greatly reduced. It is not possible that there was an exchange of substances by diffusion between the urine in the pelves of these kidneys and the blood, as the concentration of both salt and nitrogen in the two fluids is vastly different.

Furthermore, it would appear that Dogs 1 and 2, in which the ureter was patent, had a urine of entirely different composition from that of Dog 3, in which the ureteral opening was closed. The considerable amount of pus, mucus and albumin (6 grams per liter) distinguished this last urine from the former ones; the concentration of salt was much higher and that of nitrogen much lower, indicating that the urine was excreted under entirely different conditions when the uretero-venous anastomosis was patent than when it was closed, and that in all probability some urine was passing into the blood stream while the ureter was open.

The average duration of life for dogs after a double nephrectomy or a double ureteral ligation is from four to five days. In this series it was 6½ days after the second ureter was anastomosed into the venous system. The dogs became drowsy and toxic, and for a short time before death refused to eat or drink. Marked oedema before death was not noticed in any case. At autopsy one dog presented moderate oedema of both legs and body.

#### CONCLUSIONS

1. The technique by which uretero-venous anastomosis may be successfully accomplished, allowing of a ureter which remains patent, is described.

2. After anastomosis of the ureter into the vena cava the blood does not flow back into the pelvis of the kidney.

3. By anastomosing a ureter into the portal or splenic vein the effect of the urine on these organs could be studied.

4. Uretero-venous anastomosis leads to hydronephrosis unaccompanied by marked histological changes in the kidney the effect of the urine on these organs could be studied.

5. The dilation of the ureter in these cases begins at the point of anastomosis and ascends to the pelvis of the kidney.

6. After a single anastomosis, the life of the dog, at the end of two months, remains unaffected. The urea and non-protein nitrogen of the blood rises slightly at first but show no tendency to increase subsequently. When both ureters have been anastomosed into the systemic venous current, the blood urea and non-protein nitrogen continue to rise until death, about as rapidly as they do in cases of double nephrectomy.

7. The hydronephrotic kidney secretes urine which is characterized by a low salt and a high nitrogen concentration.

8. After double uretero-venous anastomosis the average life of the dogs in this series was 6½ days. The kidneys apparently do not reduce materially the toxicity of the substances which they remove from the blood stream.

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## OBSERVATIONS ON BIRD MALARIA AND THE PATHOGENESIS OF RELAPSE IN HUMAN MALARIA<sup>1</sup>

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The study of infectious diseases in certain of the lower animals has given us a large amount of information regarding infectious diseases in man; and this has been especially so in the case of infections with protozoa and worms. By taking advantage of the parallelism of such infections in man and the lower animals one has a constant supply of fresh material, and can carry out inoculation experiments which are important in study as well as in teaching.

In the study of human malaria, important information has been obtained from the study of bird malaria. Ross worked out the cycle of *Proteosoma* in mosquitoes when it was not convenient for him to work on human malaria. MacCallum first observed the fertilization of the macrogamete by the microgamete in *Hæmoproteus*. In both cases the work was later confirmed for the human malarial parasites.

My object in undertaking this study was to try to correlate the points we know in the life cycles of various parasites of the red blood cells; and to try, in that way, to get an explanation of relapse in human malaria. *Proteosoma* closely resembles the human malarial parasites, and it is convenient to work with; for these reasons I chose *Proteosoma* for my work.

### BIRD MALARIA

From the work of Schaudinn, Novy and MacNeal, the Sergeants, and Aragao, it appears that more than one type of life cycle may be included in the present genus *Hæmoproteus*. Aragao's work has given us an understanding of the cycle of *Hæmoproteus columbæ* in the vertebrate host.

In *Hæmoproteus columbæ* schizogony takes place in the leucocytes (or endothelial cells) in the internal organs, especially in the lungs. Only gametocytes are found in the red blood cells; a bird once infected is proof against further infection; and the infection is not transmissible by injection of blood. The infection is transmitted by a hippoboscoid fly.

Thus we see that while *Hæmoproteus* is well suited for studying the behavior of the gametocytes, it differs from human malaria where both the schizonts and gametocytes are in the red blood cells, and the disease is transmissible by injection of blood.

On the other hand, *Proteosoma* is like the human malarial organism, in that the schizonts and gametocytes are in the red blood cells, the infection is transmissible by injection of blood, and the intermediate host is a mosquito.

In the earlier study of *Proteosoma* it was considered that the schizonts persisted for a considerable time, but that they finally disappeared and the bird was immune.

Wasielewski showed that the schizonts persisted in the blood for from 3 to 5 or even from 9 to 11 months, because it was found possible to transmit the infection by injections of blood up to that time. From a bird in which parasites could not be found in the peripheral blood, 0.15 c.c. of blood divided among three birds infected only one. Wasielewski also found that the parasites were more numerous in the heart's blood than in the peripheral circulation.

Moldovan showed that occasionally birds recovered as early as one month after injection, but that usually there was a chronic infection up to six months with all stages of the parasite in the peripheral blood.

One of my problems was to determine whether the parasites were constantly in the peripheral blood in a form in which the infection could be transmitted by injections of blood; and, if so, how long they remained there.

The work was done with a strain of *Proteosoma* that was obtained from sparrows in New York in August, 1913, and has been carried in canaries up to the present time. This strain was obtained and used primarily for teaching purposes.

The method of procedure was to take blood from a wing vein of the infected bird, dilute it with physiological salt solution and inject it into the thoracic cavity and into the breast muscles of a clean bird. Parasites can be found in the peripheral blood up to four or five months after infection:

<sup>1</sup> Read at the meeting of The Johns Hopkins Medical Society, December 3, 1917.

after that I have rarely succeeded in finding them. But peripheral blood from an infected bird, when injected into a clean bird, has always transmitted the infection. Peripheral blood taken from a number of infected birds from month to month and injected into clean birds has not once failed to infect. The longest I have been able to follow the infection in any birds was in three birds for 29 months from the time of their infection. These birds were injected on May 14, 1914, and the last transference of blood from them was on October 12, 1916. During this time, many birds were injected with blood from the wing vein of these birds, and in every case the injected bird became infected. All birds injected with blood from these birds on the latter date became infected. All three of the old birds died before the time for another blood transference.

From this work it appears that the parasite of bird malaria is constantly in the peripheral circulation in a form which will transmit the infection on direct injection into clean birds; and that this form of the parasite is present for at least 29 months after infection.

#### IMMUNITY

Bound up with this is the question of immunity. Koch, Ruge and others were of the opinion that one attack of *Proteosoma* infection conferred immunity, and that the increase in number of cases of the disease in the spring could not be accounted for by relapses.

Wasielewski did not agree that there was immunity. After the injection of blood from infected birds into birds whose peripheral blood had been free from parasites for 4 days, 14 days, 3 months and 9 months, he was able to find on the fifth day a few parasites in the peripheral blood of the supposedly recovered birds. In three birds the number of parasites was so small that it was even possible they were only the injected parasites: the fourth bird showed from 20 to 30 parasites in specimens taken from the eleventh to the fourteenth day. Wasielewski was not sure whether the case was one of a mild relapse or of a mild new infection; but he did consider that it showed the bird was not immune.

Moldovan showed that recovered birds were susceptible to infection just as much as birds that had never been infected, but chronically infected birds were resistant against superinfection.

#### RELAPSE

In chronically infected birds there is not much change in the number of parasites in the peripheral blood, and spontaneous increase of the number of parasites has not been observed. Wasielewski often noted an increase in the number of parasites in the blood of his birds during intercurrent infections of some other sort.

Moldovan was able to produce relapses by the injection of blood of rice-birds; it made no difference whether or not there were parasites in the blood of the rice-birds.

In Wasielewski's experiments which he considered as showing that there was no immunity in recovered birds, he got only

a few parasites in the peripheral blood of the supposedly recovered bird after an injection of *Proteosoma* material. But Moldovan showed that recovered birds developed a rich infection and in the usual time, just as did fresh birds, after an injection of *Proteosoma* material.

I injected blood from one 29-month infected bird into another 20-month infected bird. On the twentieth day one parasite was found in the peripheral blood of the injected bird. A previous injection of blood from each bird into a clean bird showed that the peripheral blood of both birds contained *Proteosoma* in a form that would transmit the infection to clean birds in the usual way.

One bird, which had been injected with *Proteosoma* four months previously, showed one partly grown parasite in the peripheral blood in a 10-minute search with a  $1/12''$  objective. This bird was given an injection of blood from a clean bird. On the fifth day this bird showed no parasites in the peripheral blood on a similar search; on the twelfth day it showed one parasite in the peripheral blood on a similar search; this bird died on the seventeenth day, before another examination was made.

At the same time, the clean bird used in this experiment was given an injection of blood from the infected bird used in this experiment. On the fifth day this bird showed no parasites in the peripheral blood in a 10-minute search with a  $1/12''$  objective; on the twelfth day it showed a few parasites in the peripheral blood; and on the seventeenth day there was a rich infection.

One bird that had been injected with *Proteosoma* four months previously showed no parasites in the peripheral blood in a 10-minute search with a  $1/12''$  objective. This bird was given an injection of human blood. On the fifth and twelfth days it showed no parasites in the peripheral blood on a similar search; on the seventeenth day there was a fair number of parasites in all stages of development in the peripheral blood.

One bird that had been injected with *Proteosoma* 21½ months previously showed no parasites in the peripheral blood in a 10-minute search with a  $1/12''$  objective. This bird was given an injection of human blood. On the fifth, twelfth and seventeenth days, this bird showed no parasites in the peripheral blood in a 10-minute search with a  $1/12''$  objective.

#### SUMMARY

Thus it appears: (1) that in *Proteosoma* the usual thing is for the bird to develop a chronic infection which may last at least 29 months; (2) that all stages of the asexual cycle are found in the peripheral blood as long as any parasites are found there; (3) that the parasites are constantly present in the peripheral blood for at least 29 months in a form that will transmit the infection by the injection of blood; (4) that relapse occurs as a result of lowered resistance from intercurrent infections, or of the injection of foreign blood; and (5) that immunity lasts only as long as the bird remains infected.

## DISCUSSION

Is the asexual cycle present in the peripheral blood throughout the infection? Since the asexual cycle is present as long as we are able to find any parasites, it is very probable that it is there throughout, but is not found on account of the shortcomings of our methods of direct examination.

Then, the fact that the infection is transmissible throughout the course by the injection of peripheral blood makes it probable that the asexual cycle is present in the peripheral blood throughout the infection. In a *Hæmoproteus* infection, in which schizogony takes place in the internal organs and only the gametocytes are present in the peripheral blood, the infection is not transmissible by the injection of blood. The same difference holds for *Babesia* and *Theileria*: in *Babesia* the schizogony takes place in the red blood cells, and the infection is transmissible by the injection of peripheral blood; while in *Theileria* the schizogony takes place in the internal organs, only the gametocytes are present in the peripheral blood, and the infection is not transmissible by the injection of blood. We shall get some further help on the question from a study of human malaria; and the question of some special or resistant form of the parasite can be taken up then.

## HUMAN MALARIA

When we come to study human malaria, we do not have the assistance of animal inoculations. But we are able to study the peripheral blood some months after the last attack of malarial fever; and in this way we may get at the question of whether the asexual cycle continues during the period between relapses.

It is not unusual to find gametocytes in the blood of man several months after the last attack of malarial fever; and as a result of finding parasites in the blood of men in the spring, before mosquitoes are able to transmit them, we have come to the belief that man and not the mosquito carries the malarial parasite through the winter. Gametocytes are commonly found in the blood of these "carriers" in the spring; and it is generally agreed that the gametocytes are intracorporeal.

Rowley-Lawson holds that the human malarial parasites are extracorporeal and that they migrate from one red cell to another. The sporozoa are intracellular parasites. Aside from the points in human blood that indicate the malarial parasites to be intracorporeal, there are some points in other parasites of the red blood cell that would indicate that the malarial parasite is intracorporeal. *Protozoa* crowds the nucleus of the red blood cell to one side as it grows; *Hæmoproteus* curves around the ends of the nucleus of the red blood cell as it grows; the *hæmogregarines* curve around the ends of the nucleus of the red blood cell, coil up beside it, or crowd it to one side, as they grow.

The lowest estimate of the rate of death of the red blood cells would make the life of a red blood cell 55.5 days. Other estimates would make it as low as 23 days.

Since we do not believe that the gametocyte is able to travel from one red blood cell to another, we must conclude that any

gametocyte found came from a schizont less than two months before. So, if gametocytes are found in the blood six or eight months after the last attack of fever we must conclude that the schizogony continued for at least four to six months after the last attack of fever.

Craig found malarial parasites in the spleen of patients who had died of some disease other than malaria, and in whom there were no symptoms of malaria. The parasites were undergoing normal schizogony in the spleen, but in numbers insufficient to produce clinical symptoms.

It appears, then, that in human malaria, just as in bird malaria, schizogony continues for a long time in the chronic infection. Whether the schizogony continues in the peripheral blood or in the blood in the internal organs makes no difference in the part it can play in relapse.

## THEORIES OF RELAPSE

There are several theories as to the pathogenesis of relapse in malaria.

(1) Schaudinn considered that relapse was due to parthenogenesis of the macrogametocytes which persisted in the blood and internal organs of the patient.

Moldovan says that he undertook his experiments in order to determine whether relapse was due to parthenogenesis of the macrogamete as claimed by Schaudinn. He says that the establishment of the continuation of the asexual cycle of *Protozoa* in the chronically infected birds made it unnecessary for him to study the question further along that line.

In *Protozoa*, the asexual cycle takes place in the peripheral blood, the infection is transmitted by injection of peripheral blood, relapse occurs, and there is no immunity.<sup>2</sup> In

<sup>2</sup> Since writing this I have read Sergent and Hemphill's article in *Bull. Soc. path. exot.*, 1917, X, 550, *Sur l'immunité dans le paludisme des oiseaux*.

*Protozoa*-containing material was injected intraperitoneally into five canaries, at least two and one-half years after their original infection. One of the birds developed a severe infection, as did two controls. In one of the injected birds, no parasites were found after the injection, in three of them an occasional parasite was found. Sergent and Hemphill conclude that, in four of the birds, a relative immunity had persisted for at least two and one-half years.

It is my opinion that had they injected blood from the five canaries into other canaries, they would have found that the four resistant birds were still infected, *labile infection*, and the bird which developed a rich infection was the only one that had recovered from the infection of over two and one-half years before. The occasional parasites found in the blood of three of the resistant birds were the ones that regularly circulate in the peripheral blood of birds that have a labile infection, and the parasites were found as a result of the prolonged search made at this time; or there may have been a mild relapse as a result of the injury on making the injection.

Since superinfection is not possible in labile infection, which is so common in protozoan infections, failure to infect by injection of infectious material cannot be interpreted as meaning immunity in these infections. Recovery must be determined by injection of blood from the supposedly recovered bird into a susceptible bird.

The conditions as to immunity and reinfection in syphilis are parallel with the conditions here.



*Hæmoproteus columbæ*, the asexual cycle takes place in the internal organs, only gametocytes appear in the peripheral blood, and the infection is not transmitted by injection of peripheral blood; the question of relapse or recovery with sterile immunity is not cleared up; but a bird once infected is proof against further infection.

In the family *Babesiæ* we have life cycles similar to those of *Proteosoma* and *Hæmoproteus columbæ*, and here the question of relapse and immunity is worked out. In *Babesia*, the asexual cycle takes place in the peripheral blood, the infection is transmitted by injection of peripheral blood, relapse occurs, and there is no immunity; just as in *Proteosoma*. In *Theileria*, the asexual cycle takes place in the internal organs, only gametocytes appear in the peripheral blood, the infection is not transmitted by the injection of peripheral blood, relapse does not occur, and there is immunity.

Meyer, writing of African coast fever in cattle, says that it is impossible to infect a cow with blood containing gametocytes; that when an animal has had the disease, the gametocytes and developmental forms disappear from the blood and the organs; that such an animal is no longer a "carrier" of the parasites, and does not suffer relapse. These facts, he says, long known, are explained by Gonder's investigations, which show that parthenogenesis does not occur in *Pirosoma parvum* (*Theileria parva*). He says that, in this, *Pirosoma parvum* (*Theileria parva*) is an exception from all other known *pirosomes*.

Schaudinn's work has not been satisfactorily confirmed. And in *Theileria*, the only organism so far worked out in which it was possible to work with persisting gametocytes without confusion from a continuation of the asexual cycle, it has been necessary to note an exception to Schaudinn's theory.

(2) The theory of a resistant form of the parasite has been put forward by Celli, Craig, and recently by James. In none of its forms is this theory consistent with any idea that the resistant or resting organism is intracorpuseular, on account of the short life of the red blood cell. Again, since gametocytes appear in the blood for months after the last attack of malarial fever, we know that the asexual cycle is going on. If it is considered that the resistant form of the parasite is extracellular, or is in some cell other than the red blood cell, we can only answer that no evidence of such a form has been found in *Theileria*, the only organism so far worked out in which there is not confusion from a continuation of the asexual cycle.

James' statement of the theory of a resistant or resting stage is as follows:

1. In instances of true relapse, as distinguished from recrudescence, the first forms of the parasite present in the peripheral blood are large forms which, if seen during the course of an ordinary attack, would certainly be classed as gametocytes, though it might not be easy to say definitely to which sex they belong. These forms, and the pre-sporulating forms which follow them, are found before the patient has any symptoms, or is aware that an attack is impending.

2. In cases which relapse during, or very shortly after, vigorous quinine treatment by the mouth or intravenously, prolonged search of the peripheral blood may fail to show the presence of parasites, but examination of films of splenic blood may reveal, as if "encysted" in dehemoglobinized red blood corpuscles, (a) large forms resembling gametocytes with a voluminous nucleus; (b) similar forms with the nucleus divided into three or more separate blocks.

These are persistent forms upon which quinine given intravenously is inoperative, and, failing a better explanation, one assumes that they are the cause of the relapses, and that they are not gametocytes, but are asexual forms in which the parasite lays up during the intervals between true relapses.

If no parasite can stay in a red blood cell more than two months, it does not appear that we can accept James' suggestion that the parasite lays up in a red cell during the interval between relapse. He is probably right in saying that they are asexual organisms, but they must go through their cycle in less than two months or be lost.

James' description of these parasites sounds like Prowazek's statement regarding the parasites that are found in chronic bird malaria. Prowazek says that, while in chronic human malaria we find mainly gametes, in chronic bird malaria we also find young parasites of which one is not able to say whether they are young schizonts or gametes.

Moldovan's statement that if we can demonstrate the continuation of the asexual cycle we do not need to study the question of whether relapse is due to parthenogenesis of the macrogametocyte applies equally to the theory of a resistant or resting form of the parasite.

Intracorpuseular conjugation, as described by Craig, can be interpreted as a method of keeping the asexual cycle active as readily as a method of producing a resistant form of the organism. We know that asexual reproduction can go on for years in various protozoa, as shown especially for *Paramecium* by Woodruff and Erdmann. The strain of *Proteosoma* with which I have worked has been carried for over four years without going through an arthropod host. That some nuclear rearrangement takes place seems to be very probable, and intracorpuseular conjugation of parasites may be of the same nature.

(3) Bignami states that

in all probability relapses, whether at short or long intervals, or whether separated by lengthy periods of latency, should be considered from a single viewpoint; that is to say, as having the same genesis, depending on the persistence of the pyrogenous cycle. In one group of relapses the parasitic material that maintains the infection is represented by a minimum quantity of forms of the ordinary fever-producing cycle, often recognizable by an accurate microscopical examination, at least at some time in the course of the infection, which forms for a long time cannot attain the quantity or the virulence necessary to cause fever. Especially in those cases in which a series of relapses occur at longer or shorter intervals without quinine treatment, one should keep in mind the possibility that after a series of febrile attacks the organism acquires a certain immunity in respect to the pyrogenic action of the parasites; which immunity being transitory, as happens in other infections, it is attenuated or ceases after a certain period of apyrexia; whence the onset of relapse.

But there is also a group of relapses, in which the material, which maintains the infection during the period of latency, is represented by forms resistant to quinine, due to a process of selection under the action of the alkaloid, as occasion offers; it is not necessary to suppose that such forms differ morphologically from others as I, myself, more than once, have also thought.

In my opinion, all of the findings are in accord with Bignami's view, that is, that the asexual cycle persists during the period between relapses; that during the period between relapses the organisms are present in too small number to produce symptoms or to be found in the peripheral blood; and that when something happens to reduce the resistance, this cycle becomes more active, and the organisms become numerous enough to produce symptoms and to be found in the peripheral blood.

The continuation of the asexual cycle over long periods in which there is no clinical malaria is undoubted. Relapse does not occur in infections with the only organism worked out under conditions where it is possible to observe persistence of gametocytes. No resistant or resting intracorporeal form of the organism can exist for more than 50 to 60 days, on account of the short life of the red blood cell.

Bignami considers that there is some change in the biological properties of the organisms that carry on the low grade asexual cycle and are resistant to quinine. I believe that there is something more to the immunity of the host than "in respect to the pyrogenic action of the parasites." That is, I think there is more than immunity to the *paroxysmal toxin*. Schilling is of the opinion that the *paroxysmal toxins* do not have any appreciable antigenic action. In cases not treated, not only do the attacks of fever become milder and finally cease, but the parasites become fewer and fewer in the peripheral blood. This is readily followed in *Proteosoma* infection of birds, and is a common observation in human malaria. Then, in *Proteosoma*, the infected bird is resistant to superinfection, even though no parasites can be found in the peripheral blood. I believe that antibodies are produced which actually oppose the growth and multiplication of the parasites; that in some cases this opposition is strong enough to actually destroy the parasites and recovery results; that more commonly the opposition is not strong enough to destroy the parasites, but a few of them become resistant and keep up the cycle—what Schilling calls *labile infection* (Plehn's *tolerance*). Here the animal resists superinfection. When anything occurs to lower the resistance of the host, these parasites multiply rapidly and set up a relapse. Here, as in so many other protozoan infections, the antibody production continues only as long as the infection exists: as soon as the infection ceases, the stimulus to antibody production is withdrawn, and the animal is again susceptible to infection.

#### CONCLUSION

In malaria, the body produces antibodies which resist the multiplication of the parasites. But certain of the parasites become resistant to these antibodies (or to quinine) and continue the asexual cycle, the number of parasites, however, being too small to produce symptoms. When anything hap-

pens to lower the resistance of the body, these parasites are able to multiply rapidly and produce symptoms; that is, a relapse. The continuation of gametocytes is due to the continuation of the asexual cycle. As long as the infection continues, the body is stimulated to produce antibodies, and the infected person is resistant to superinfection; that is, there is a labile infection. There is no immunity after recovery: as soon as the infection is stopped by the antibody production, or by treatment, the stimulus to antibody production is withdrawn, and the person is susceptible to reinfection, just as though he had never been infected before.

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#### DISCUSSION

DR. MACCALLUM.—I want to congratulate Colonel Whitmore upon this splendid paper which puts the whole thing in a much clearer light than it was before. There were two or three points that struck me particularly. One was the reference to the question as to whether the parasites are intracellular or not. I am sure there is no possible doubt about that. You can see them inside the corpuscles, see them move inside the corpuscles, see them move the nucleus and see the corpuscle break and the parasite come out, sometimes dragging the nucleus out.

The question of relapse is a most important one. I gathered from Colonel Whitmore's paper that it is his opinion that the asexual cycle is the thing that is responsible for the relapse. Colonel Whitmore's statement about the inability of these organisms to superimpose themselves on an old infection is especially interesting. Does that mean that no amount of introduction of new parasites, even of the same character, in case resistance is lowered, will "take" in such a person? In that case it is interesting to consider what has happened in those persons who die of an acute attack of malaria. You almost invariably find there are signs of long continued infection. Are we to understand that in those cases there has been one infection from the very beginning, and that they died from an acute attack merely because through some indiscretion they have lowered their resistance and have become subject to an exacerbation of their original infection? If that is so, it would mean, I suppose, that a person can have only one infection, in fact is practically immune then except for his original malaria.

I might say a word about the existence of malaria in some of the countries I visited last year. It is the disease in those tropical countries, especially in the East Indies. I think that cholera, plague and leprosy sink into insignificance compared with malaria. In the Malay States, for example, I found that the coolie laborers died off at an astounding rate. The engineer of public works at Kuala Lumpur told me he was in the habit of hiring 100 coolies at a time, different kinds each time. For instance, he would start with 100 Chinese coolies; 85 per cent

would die off in a few days' time and the rest would run away. He would then try Malays and so on, but 95 per cent was the average of deaths. I did autopsies in Singapore for about 17 days and in that time I had 11 cases of fatal malaria at autopsy. In all my previous life I had seen only four fatal cases. These 11 cases were chiefly of the æstivo-autumnal, or subtertian type, as the English call them. The material, microscopically, proved to be most interesting. They were apparently cases of massive infection. The intestinal mucosa showed the capillaries completely plugged with organisms. In the brain also the capillaries were found to be completely plugged with parasites. I suppose that was largely responsible for the coma in which these patients were plunged toward the end.

LIEUT.-COLONEL WHITMORE.—I was very glad to hear Dr. MacCallum express himself so definitely that the parasite is intracorporeal. That is an important thing for our argument.

The question of superinfection seems to be rather a broad one. The idea seems to be that the body has developed antibodies, and only certain of the parasites have become resistant; and they are able to live and complete their cycle just balanced by the antibodies; that is, we have a labile infection. Wasielowski was not able to say definitely in three of his birds whether the parasites circulating in the blood might have been the ones he injected. It is generally considered that in the protozoa, superinfection is not possible so long as infection lasts.

The question whether a man can have malaria more than once in his life is not so easy. Koch applied his immunity idea to human malaria and considered that in malarial districts the children who had the disease become immune, and for that reason we did not have malaria in adults. I think it is definitely agreed now that that is not the case; but that in those people who have had malaria as children, chronic malaria persists and that is why they do not have malaria as adults. They have a chronic (or labile) infection and are resistant to superinfection.

I would hate to feel, however, that with all of our treatment we do not cure any cases of malaria. Moldovan showed that occasionally birds recover. Of course, we have followed Proteosoma in birds for only 29 months, and that is not a very long time in the life of a man. Whether a man may be infected for a few years, and then recover, is pretty hard to say. In malarial districts, a great many people seem to recover, but apparently many of them remain infected. If they do recover, they get another infection right away, and always keep one going. In one place in Colombia, where we had occasion to go to look into some supposed yellow fever, it happened to be convenient to get blood from 10 persons—men who had not had malaria for months. In four of those 10 we were able to find malarial parasites in the peripheral blood without prolonged search; so I am inclined to think that those people have an infection almost constantly.

## THE PHYSICIAN'S APHORISMS: A MEDIÆVAL HEBREW SATIRE

By HARRY FRIEDENWALD

Hippocrates was greatly revered during the middle ages by the Jews. He was called the "Chief of Physicians" by Maimonides and he was spoken of as "The Saint" (*He-Hasid*). His works were variously put into Hebrew from Arabic or from Latin translations and they were provided with Hebrew commentaries.<sup>1</sup> It is an indication of their popularity that a

Hebrew satire was written in the form of the aphorisms under the title "The Physician's Aphorisms."

The author was En Maimon Galipapa,<sup>2</sup> a Provençal, of whom nothing is known but that he wrote satires (probably in the latter part of the 13th century), the one just mentioned and "A Widow's Vow," and "The Contentions of a Wife."

<sup>1</sup> See Steinschneider, *Hebraeische Uebersetzungen*, Berlin, 1893, p. 688.

<sup>2</sup> Concerning authorship, etc., see Davidson, *Sefer Shaashuim*, p. 119.



These works have been edited and published under the title "Three Satires" by Prof. Israel Davidson (New York, 1904), from "a unique copy in the Bodleian Library at Oxford."

Following the form of the Hebrew translation of Hippocrates, in which each chapter opens with the "Amar Abucrat" (*i. e.*, "Hippocrates says"), each paragraph of the satire begins with the words "Amar oyeb" (*i. e.*, the "Enemy says"). The Hebrew style is that much in favor at that period—the use of Biblical expressions and phrases woven together.

In the translation<sup>2</sup> which follows there is no attempt to indicate the Biblical references excepting in the first paragraph.

#### THE PHYSICIAN'S APHORISMS

Oyeb (the enemy) said: "I will pursue and overtake [Ex. XV, 9] the worthless physicians [Zach. XI, 17 "worthless shepherds"]; they rejoice with the joy of harvest [Isaiah IX, 3] and as one gayly tripping to the music of the flute [Isaiah XXX, 29], when they slay a man before his time [Job XV, 32] and he is cut off from his people [Leviticus XVII, 4] and his place knows him no more [Psalm CIII, 16]. I will tell of their wicked ways, their evil shall be disclosed, they who bring misfortune upon misfortune [Job XVI, 14], they who are corrupting the world [I Samuel VI, 5]. I will conceal my name, lest they should curse me, lest in a short while they should stone me [Exod. XVII, 4].

"Whoever reads one chapter of this every day will abide in safety, and without fear; he will find repose for himself when his head aches; and if he knows it by heart, it will be a cure for all his flesh."

#### CHAPTER I. GALE OF VANITY

1. Oyeb said: "Life is vanity; labor is regarded with disfavor; they who should work, shirk; and time presses.<sup>4</sup> Practice distresses; the sick are foolish and put their trust in a physician, a heretic or an atheist; those that aid him are stupid, leaning toward crooked ways. There is a time for life and for death, for cure or for the shadow of death. There is no controlling God's action! Who will be rejected? Who will be spared?"

2. Oyeb said: "When one is ill let him not seek the physician; whether he be strong or weak, do not desire his remedies. Avoid his paths, be careful lest he visit you, for one dare not expect a miracle. He comes with haughtiness and arrogance in order to increase the trouble. Woe unto the patient with whom the physician comes in contact, for seven abominations

<sup>2</sup> I desire to express my gratitude to Professor Davidson for his advice and his revision of this translation, as also to Dr. E. N. Rabinowitz, Dr. L. M. Palitz, and Dr. David Blondheim for their help.

<sup>4</sup> Compare with the words of Hippocrates' Aphorisms: Life is short and art is long; the occasion fleeting, experience fallacious, and judgment difficult. Compare likewise with "Sayings of the Fathers" (II, 20) The day is short, the work is great, the laborers are sluggish, etc.

are in his heart. He winks, he gestures with his fingers; to increase his fee is his only thought."

3. Oyeb said: "The foundation of medicine was brilliant wisdom and its ways were upright. Recently, however, new people have come; the present doctors, who have learned little, boast: 'We are wise and know all the secrets of science,' but they are ignorant and empty-headed. They only take the gold the silver, the coin. They corrupt and do evil, but how to do good they know not."

4. Oyeb said: "At the first visit of the physician he says: 'Why are you lying down? Arise if you wish that your illness and your aching shall pass away; avoid wine and lust; likewise eat no meat, and subdue the desire of your stomach; eat nothing but barley food, which is healthy for asses, or a little bread with lentils and soup.' So spoke the physicians who were gathered in Bene Berak, that the fever might vanish. But the fever increases with pain, like a blossoming flower. The physician will promise to cure, but there is no assurance."

5. Oyeb said: "The doctor makes great pretense; he draws the patient's arms once to the left and then to the right; he says to the pulse, that it is good, but he is as a blind man who gropes about at midday. Once he will say that the patient is leaping over mountains, then that he is walking in the plains [*i. e.*, he is constantly contradicting himself]; there is no truth in his words; he is not able to distinguish his right hand from his left!"

6. Oyeb said: "Concerning the color of the patient's urine, the fool will speak deception and falsehood and will tell many lies. He will ask to look at the color, to determine whether the sickness is in the body or in the bones, for 'his waters deceive not' [Isaiah LVIII, 11]. He shakes the urinal; he sees whether the sediment is above or at the bottom, and whether it is red. When its appearance is red, he will sentence to death; he will look at it with sadness. But if it is white and cloudy, he will likewise say there is no hope. He sees but darkness and chaos."

#### CHAPTER II. A GALE OF RIDICULE

1. Oyeb said: "There are four kinds of humors<sup>5</sup> which are the foundation of the man's constitution, to enable him to walk abroad with his staff (Ex. XXI, 19). The temperaments produced by these humors are eight, good and bad. Each of these is opposed to the other. If there is peace among them, the body is healthy, there is no need for the doctor, for drugs nor for remedies. But when one property rises against the other, then the person takes to his bed and his visage is marred."

2. Oyeb said: "There are three kinds of fevers; in the humors, in the limbs, and in the spirits, and from these the fever spreads either for life or death; likewise all disease and pain, whether cold or hot, arise from these. But it is not worth while to call the doctor to aid, for he will say to himself:

<sup>5</sup> The four elementary juices in Hippocrates' medicine were blood, phlegm, yellow bile and black bile.

'I shall become renowned if the patient's life is saved;' yet he is ignorant and willing to do a wrong."

3. Oyebe said: "In a continuous or daily fever, all that the physician does is falsehood and pretense and in tertian and quartan and complicated fevers [he is guilty of] thousands and myriads of errors. But what does it matter to the physician whether the patient dies or lives, so long as he gets his fee; and the result of his work, let it be what it may."

4. Oyebe said: When one is very constipated, the physician puts a syringe in the rectum, and gives an injection without rule or measure, in order to separate the 'bitter waters' and the fæces; while the syringe is still in place, the doctor thrusts it further in; the patient cries aloud and cannot endure it, but the doctor says: "Keep quiet, until the mass is out. Why shall you remain constipated? Wherefore shall you die before your time? Now you will be clean of all impurity, and you will sit in cleanliness in your house. Wherefore shall you remember the day of your going out [*i. e.*, your movement]."

5. Oyebe said: "When one has diarrhoea, is couching down . . . cannot find rest for himself, and he needs to go abroad; when cramps, pain and suffering come on, and he is afflicted with his excrement and his intestines are boiling and he fills one vessel after another, until his abdomen and flanks cleave to one another; then the physician comes, haughty and working wonders, and he says: 'To death with the movements of the bowels, for I will give a remedy and this will stop; then will [you] again become firm and harder than a rock.' But to the patient this is of no avail, as the everlasting running still continues. Then will he cry: 'Why does this one [doctor] come to increase my troubles; for he has not closed the doors of my belly?'"

6. Oyebe said: "When the head aches, and the pain is severe and the only thing is to lie abed and the patient cries: 'My head, my head, call the doctor, tell him about me; because of the headache, I am not able to taste and touch anything; there is darkness [about me] and no light! Oh, that some one might cast me into a pit or into the river, for it were better for me to die than to live; there is no hope for my desires!'" And behold, there come two asses, two physicians, ignorant of most things. One puts his hand on the patient's forehead, and the other on the back of his head, and they cause the patient to become more frightened. One says this, the other says that; and the patient continues his wailing. Then they will say: 'We need our books to find a remedy for you, that you shall again be able to raise your head!'" One anoints him with the oil of falsehood, the other gives him 'bitter waters' to drink; they will not rest until they lower him into the pit of hell and uproot him completely."

7. Oyebe said: "When one has earache, the physician will examine; then he will say that this is the illness; why should he lie? He stretches forth his hand to take his fee and place it in his pocket or his purse. Then he prepares his remedies one by one, with his instruments, ointments, and wicks; in case these do no good [for they are useless], he complains that it is the

patient's fault, 'who did not hearken to my voice and did not incline his ear to me.' Then the patient will reply: 'Behold, I remembered you when I was on my couch, and I obeyed you; and now you stumble over your own words according to which the remedy was ordered; and besides you have made me deaf.'"

8. Oyebe said: "When one has a spot or a cloudiness covering the eye or is blind, and 'Jericho was straightly shut up' [Joshua VI, 1, *i. e.*, the eye is tightly closed] and the doctor is consulted about the disease, he answers with pride and arrogance: 'Who is wise and able to explain this, and who, like me, in past or future, can interpret it? For those who suffer with their eyes, my knowledge reaches to the heavens, and for all humankind have I established my covenant. My wisdom is greater than that of the angels; when the sight becomes dim, I do wondrous work to clear it; I bring healing to the eye.' The patient's relatives honor him, they almost carry him on their hands. He visits with words of flattery and sits at the entrance of the house; he prepares in his hand the salt of Sodom and the poison of a serpent, thorns and thistles, makes a plaster of them and puts it on the eye; but this is as a sword and a spear, and the pain increases exceedingly and the patient cries bitterly, for his eye is blinded!"

#### CHAPTER III: FRIVOLITY

1. Oyebe said: "Concerning fevers in the humors, the physician will tell wonderful things to deceive people. He will proclaim all over the world, even to the islands: 'Whoever wishes to live, let him come unto me and I will give the right treatment; it has been prepared and kept since the days before Ashmedai, the king of the demons. Hearken to me, O Nations, go and eat early in the morning and taste my bread [remedies]; it is valued as a food for great and mighty kings; the onion and the garlic mixed with straw, to be eaten in abundance with dry bread. Likewise, at midday and in the evening, you shall eat the meat of abominable, creeping animals, poultry or eggs. And likewise shall ye lie with women on a full stomach; this is a secret remedy and cure. This ye shall do and live from day to day and God will be with you, and He will not permit the destroyer to come into your houses. And whoever does not believe this, will do the opposite—"A man's folly will pervert his path." When it is rumored that the plague has begun to spread, we will send people to Gilead to seek for remedies, or for wine and beer in the cave of the two daughters of Lot, for their wine is from the vineyard of Sodom and from the fields of Gomorrah; a remedy is near at hand whose virtue and value no one can estimate. But if one's bad luck causes him to die, you need not weep, neither shall you pity him.'"

2. Oyebe said: "In liver or heart or lung diseases, the physician will say: 'I am an expert in their treatment, and I have acquired much wisdom and knowledge; this is known over all the world.' But in truth he is like an ass under a pack-saddle when he opens his mouth with words of frivolity. Instead of

wisdom they are [words of] stupidity and foolishness, and thus he says: 'For understanding of the liver, I surpass in knowledge and for heart disease there is no one like me except a dog; concerning diseases of the lung, who but I am sure that he knows of a wonderful cure? And on your giving me a trial, what will you find but that all the seven sciences are possessed by me?' And in truth, seven are the abominations in his heart and he has no conscience within him. Verily, while he continues in his self-flattery, the patient is in a critical condition: and though they find him to be ignorant, and put him to shame, yet will he not cease from his evil actions."

3. Oyeb said: "Go and see the doings of the physician and his remedies, for which he carries his sheaves [*i. e.*, fees]. He opens his mouth without limit, asserting that he knows all about diseases, accidents and their causes; he talks much about how to prepare aid and remedy. He goes to the druggist with pride, raises his hand to write, in order to show his ring. He prescribes in a foreign language, for his science is foreign to him; [he does this] in order to remove the crop with its feathers [in order to "bleed" the patient]; and between one word and the other he spits; this is his manner and habit. In unimportant matters he makes himself very busy. He says to the druggist: 'Take the liquid to the patient, charge him as much as you can, and ask for the pay, ere his lamp will be extinguished. And if he finds in it trouble and misery, we are innocent, since "all who spoil are exempted."'" Both rejoice in their prey, as people who have done charity. And what does it matter to them if the patient dies, for the earth will cover him! 'And what does it matter to us? We shall live on!'"

4. Oyeb said: "Listen, all ye people, to the words of the stupid quack who dwells in aristocratic places, when he says: 'I am descended from ancient kings, I am the son of sages, since the day that God created man. Who has secured even half of my knowledge in understanding the secrets of herbs, and of different drugs? Who knows their many high and low degrees? I know each one according to its name and place.'

"About bloodletting he will say: 'Did not my mind do all this? For I understand how to distinguish between good and bad hours and lucky and unlucky moments.' But he does not even know when it is new moon nor when it is full moon; he claims to know the days of bad omen, and that the day on which Haman was hanged is dangerous for bloodletting, unless it be for circumcision."

5. Oyeb said: "What a crime it is for the physician to speak foolishness in his ignorance and to extol himself with much wisdom. Woe unto such a shame! Woe unto such a disgrace! Even when one asks him about the limitations of medicine, he will answer arrogantly: 'Is any knowledge hidden from me? What sort of a question is this? There are two limits, you see, a limit on one side and a limit on the other side!' And if he is asked about fever, he will answer that this

is a burning without fuel, coming hurriedly at different times one after the other. He will declare that the law [governing the fever] is hidden with the Lord; no man will ever know it. Concerning the beginning of the disease, its progress and disappearance, who can understand its nature and its duration and its end; all his words are void and vanity."

6. Oyeb said: "A physician's mistake leads to crime, quarrels and disputes. Of the dead he says that he is alive, and of the living that he is dead; there is no truth in his speech. He is the Reaper's agent; he is the assistant of the Angel of Death and his messenger; this is his function. He gathers medical books new and old and of many kinds to make a show of them, but not to read them. And if there are errors in them, he does not discover them; they remain where they are, there is no one to correct them. If he is asked about a chapter or a good treatise, he will put off the answer for the morrow, and at an opportune time he will say: 'Go away, go home, do you wish to examine me? Shall such a man as I answer fools? I am the physician who cures all maladies!'"

7. Oyeb said: "This is the way the present doctors slaughter, in order to get large fees and to be regarded as experienced. For the instructors announce: 'Whoever practices medicine without getting fees deserves to be stoned. Learn to make money by analogy from the Field of Ephron, [as Ephron, the son of Zohar, took from Abraham 400 silver shekalim to bury Sarah]; thus you will reap benefit and save. Go ahead and take for yourself, slaughter your sacrifice, and so eat [your fill]. Be ready to visit the patients, but not for mere talk or to be their aid and protector; for large compensation only and not for nothing! Here you have an example: King Hezekiah hid the book of medicine, because the physician did not get the reward of his labor. They would put off payment saying: 'Wait until Shiloh (Messiah) comes; go home in peace, but dare not to come here to ask for your reward.' Therefore, be careful in your practice, and do not come to the patient's house until you get your heave offering; and do not leave the house with empty hands, or with only some eggs or a piece of bread.'"

#### CHAPTER IV. DECEIT

1. Oyeb said: "Now let us describe all the remedies and their order, which were established in the days of Terah [father of Abraham] in Haran. A liquid medicine for fevers, and it is like sharp swords. Let there be taken roots of broom-bush and grass of nets, and the flowers of priesthood, from each one a part; a withered leaf and a leaf of thought, from each one an ounce or a pound; the shell of garlic, beans of the garden, a rod and a bullrush and foam also, from each one and a half pint, filled or empty; wasp's honey and the braying of an ass, and the threads of net; the mucus of the nose, the noise of millstones, from each one a handful; all this put in a pot, perforated or broken; let it be cooked with cursed water on the fire of hell [you can obtain it gratis] until it has boiled down one-half, and then it will be ready to drink. One bowl of foam and a pitcher of water let him drink at twilight.

\* A Mishnaic law that exempts destruction of an object on the Sabbath from the penalty imposed for work done.



and let [the sick] taste of it at dawn. This cup of swords will empty him, without leaving a remnant until the intestines drop out; and, when he looks at the cup, his abdomen will swell.

2. "Another general remedy for all diseases: Let there be taken the mouth of a serpent, the noise of a storm, the blackness of the Ethiopian, the whiteness of women, oil of quarrel and contention, from each one-half measure; the tail of a lizard, the twittering of birds, the base of a camel's hump, the wings of flies, and the brain of a flea, and a whole fat tail, and the blossoms of shame and reproach; this you must cook; boil it in presumptuous water, with the eggs of lice, from each two kinds, in a boiling kettle full of crushed things and it shall be kept boiling until the water turns to vapor; let [the sick] drink it in the evening, morning and noon, and whether he will find a cure for his malady in the end will show, especially after his death."

3. Oyebe said: "This prescription will help in every fever, also in any illness or abscess: Take pure frankincense and powdered dust, thorns, soot of a furnace, and much smoke, from each one an equal measure with menstrual blood and the liquid part of feces and thin dirt and feces of wild foxes, from each one five shekels; oil of hypocrisy, and shame and reproach, and bitter spices, from each one a manah; perforated baskets, deadly venom of a poisoning snake, semen of evil doers, occipita of frogs, cow's dung and deadly flies, juice of brook-stones, and soup of putrid flesh, of each one an equal weight; after the art of the apothecary shall they be mixed. All who eat it will do evil and will become heart-sick when they take it."

4. Oyebe said: "In the valley of weeping on the night of the Ninth of Ab, when the lamentations are being read, the doctors of the present day prepare the oil, to anoint the heads of the Am ha-Aretz [ignoramus] so they can fleece them: First take salt of Sodom, falsehood and deceit, poison of serpents and the head of an asp, and the water of those who have

to bring offerings for transgression; nets and thorns of vineyards, and powdered dry grass, oil of burning, sweat of a tired person, from each one a tenth of an ephah. Together with all these, pound the wicked fool in a mortar, with crookedness; and this shall be the ointment. Whoever is rubbed with this will have sorrow and groaning instead of joy; he will have sickness instead of gladness, he will hope for cure, but, behold, there will be terror.

"This was written and signed by the scribe of the city; all of it by his strength and of his might; who can bear it, for it will be as a stumbling-stone? With it he will dig for himself his own deep grave."

#### CHAPTER V. PEACE

1. Ohebe [the friend] said: "Now I repent, if I have spoken badly about the physicians, for I meant well! To wake their conscience; to make them study better their medical books [is my sole purpose]. Let them but be correct in their work and strong. Let them not waste their days in vanity and deceit. Let them walk before the people with courage; from this day on there shall be peace [between us]. I will tell no more of their shortcomings. From having been their foe, I will again become their friend; it is I who am speaking to them!"

2. Ohebe said: "We are tired of many words. Let us make peace between us and become friends. If I have spoken till now because of my sorrow and anger, let friendship return and I myself shall lead it. If I have spoken too much, all will again be good and calm like the waters of Pishon. And you physicians, do your work diligently and with clean hands; and take for yourselves silver or gold, for the living must die and the dead will be restored to life. Seize fortune when it deals pleasantly with people. I have found a noted proverb, and it shall be as a sign to you: 'Good fortune comes not to the faithful man.'"

## MINUTE ON THE DEATH OF DR. THEODORE C. JANEWAY

ADOPTED BY THE MEDICAL BOARD OF THE JOHNS HOPKINS HOSPITAL OF MONDAY, JANUARY 7, 1918, AND PRESENTED TO THE BOARD OF TRUSTEES

It is with a sense of sorrow and of personal loss that the Medical Board of The Johns Hopkins Hospital record the death of Theodore Caldwell Janeway, for a little more than three years the physician-in-chief to the hospital.

Dr. Janeway was a marked man from the beginning of his medical career. He was a lecturer in medicine first at the Bellevue Medical College and later at Columbia University where, in 1909, he was chosen Bard professor of medicine. He was at different times visiting physician to the City Hospital, St. Luke's Hospital and the Presbyterian Hospital in New York. In 1914, he was called to Baltimore to become professor of medicine in the university and chief of the medical clinic. In these positions he served until his death. Born on

November 2, 1872, he died of pneumonia on December 27, 1917, at the early age of 45.

His natural medical ability he inherited as the son of a distinguished physician, but he acquired also from long and sympathetic association with his father a passion for medicine as an intellectual pursuit and an appreciation of it as a means of benefiting and assisting his fellow man. He was thus peculiarly fitted to serve as the head of a medical clinic, for to his great medical skill and judgment was added deep sympathy for suffering humanity.

The knowledge of medicine brought to him a sense of responsibility which was not to be satisfied solely by the treatment of patients under his care in the hospital or dispensary.

He keenly felt the economic and physical distress so frequently associated with and resulting from disease, and he gave to many charitable associations freely of his time and advice in the attempt to improve the condition of the unfortunate. He worked tirelessly and without regard for his health or strength.

A natural teacher, a clear, forceful expositor and an enthusiast that others should recognize the possibilities of medical science as well as the duties and obligations resting upon those skilled in medicine, he exerted a profound influ-

ence upon his students and associates and an influence that will not cease with his death.

Called into the service of the government in the spring of 1917, Dr. Janeway gave to the surgeon general's office his untiring efforts as befitting one with the high sense of patriotism that characterized him. The love of country led him to spend himself freely and to such an extent that he could not withstand the disease to which he fell a victim, young in years but having by precept and example influenced much the lives of many men.

## PROCEEDINGS OF SOCIETIES

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

OCTOBER 22, 1917

1. **Personal Observations of the Hopkins Unit in France.** JAY McLEAN.
2. **Extracts from Letters from Various Members of the Hopkins Unit.**

NOVEMBER 3, 1917

1. **Adenoma of the Recto-Vaginal Septum.** DR. T. S. CULLEN.  
Published in the BULLETIN, November, 1917.
2. **Experiences in a Base Hospital.** DR. THOMAS MCCREY.

It is always important to keep in mind that no one man sees all phases of disease in war; indeed, the great majority of men will see only one phase. Men in different places see different stages of the same disease. Practically all the patients in the base hospitals in England come from France, some only 36-48 hours from the trenches. My work was in an active general hospital of 2080 beds, with a number of associated convalescent hospitals, so that the service was constantly moving. One might think that to handle a service of 1000 medical or surgical patients would be difficult, but with proper methods it seemed little more difficult than the management of 100 beds.

In regard to the transport of the wounded, a message would come, for example, that 180 stretcher cases or 100 walking cases were on the way. The message would be received some hours ahead, and the convoy trains would come within five minutes of the specified time. The hospital trains are very well equipped, and the man in charge stops the train, when he wishes, for emergency cases. When the trains arrived, the stretchers were ready and the cases were assigned to the wards on the station platform. Every wounded patient carried on his coat a thick envelope of waterproof paper, on the outside of which was the diagnosis. There was enough on the card to indicate where the man belonged. The adjutant would look at the card and write on it the ward to which the man was assigned. The average time for a convoy of 120 stretcher cases was one hour from the time the train was in to the time the last man was in bed.

Among the diseases peculiar to war, we may first mention trench fever. This is absolutely new, so far as I could see. The vast majority of the cases come from the trenches, but a certain number have arisen back of the trenches. Statements

are made that the disease has originated in hospitals in England among nurses and orderlies waiting on patients with the disease. I was told one case occurred in a nurse in the hospital where I was. I was able to prove that this was not so, and I could not find any one who had definitely seen such a case. The patients have an onset much like any other acute febrile disease. They feel badly for a day or two, have a good deal of headache, malaise, chills, fever and loss of appetite. The fever begins comparatively early and is not necessarily high. When those symptoms develop at the front, the men are sent down at once, and I saw some of them in about three or four days after the onset. In general, there is nothing particular in the examination, except one striking thing. They complain of pain, which is generally described as being in the shins. The fever is variable; it lasts sometimes five, six or seven days, sometimes only three or four, and then drops and the temperature runs along for some days at normal. After this interval of from 5-7 days, there is a sudden elevation in temperature, the fever going up to 102°-104°. This persists for 24 hours and then drops to normal. There is another afebrile period for 5-7 days, and then another paroxysm, the temperature again dropping to normal. That may go on for seven or eight attacks. The majority of the patients had two or three: after that the temperature was normal and there was no return of fever. With this elevation of temperature, there is apparently no increase in leucocytes. The pulse always goes up a little and the patient looks very ill. The point of particular interest is the condition in the legs called "painful shin." In the majority of cases the shin is very tender. In some cases when one goes near the bed, the man implores you not to touch it, a condition I have only seen otherwise in very severe cases of rheumatic fever. If you examine more carefully, you find that they often have tenderness behind the knees. Indeed, a good many of the patients had as much tenderness on pressure behind the knees as in the shins. After the period of fever is over, there is nothing left but this excruciating pain, which is usually worse at night; and it is very common to find these men sleeping during the day. Naturally, in such a condition, symptomatic therapy is of importance, but it was not very successful. Locally, the application of a solution of Epsom salts gave more relief than anything else. I was interested in trying the effect of sunlight. It acted like magic in some cases, but un-

fortunately they were the exceptions. Some of the patients were not affected at all. The views as to the etiology are conflicting and not one has been confirmed. A good deal of evidence points to the fact that the disease is carried by lice.

A second disease which one might say is peculiar to war, is the war nephritis, in which there certainly are seen features which are different from the ordinary acute nephritis seen in civil life. These cases usually have an acute onset. Many of them do not know anything is wrong until told by their comrades that their faces are swollen. Some begin with severe headache and others have to fall out on a march on account of dyspnea; others feel weak and have pain throughout the body. In the early days edema is comparatively common, particularly of the face, and there is slight fever. One feels after watching these patients that such a case may go on indefinitely. It is called acute nephritis, but it goes on for week after week without any apparent change. The edema clears up fairly promptly. Uremia is not very common, although we had several patients brought in with it, who, when they left France, had apparently been well. After a few days, as the edema disappears, the patients feel better except for the persistence of excessive headache, which is generally relieved by lumbar puncture. The most persistent finding was blood in the urine, which went on indefinitely. It was not, as a rule, macroscopic after the first few days. There were a certain number of pus cells in nearly all these patients, and one curious thing was that the patients who had uremia were the ones who did the best. The duration in those cases was less than in the men who did not have uremia. The blood-pressure was not at all constant; in many there was a tendency to a rise during the day, often associated with the headache.

One naturally wonders what is at the bottom of these cases. A few are instances of an acute flare-up of an old nephritis, but these are only a small number. Again, one thinks of an infection from the throat. This has been studied pretty thoroughly, and it cannot be found except in a very small proportion. Pathologically, the features are exactly like those found after scarlet fever. In the majority of the cases the etiology is unknown.

One saw a certain number of cases of jaundice. We were hunting very busily for spirochetes, but did not find any. A number of cases resembled ordinary catarrhal jaundice; others were much more severe and one did not know what to call them.

One condition is going to worry every medical man in war service, and that is the cases of so-called soldier's heart. I saw nothing in these cases in any way peculiar to war. They were what we would ordinarily term cardiac neuroses, with perhaps a few additional points. There are nearly always some disturbed sensations referred to the heart. The patients often complain of pain which is a striking feature of the cases. In some there is breathlessness on any exertion and there is generally marked vasomotor disturbance, which is sometimes very striking. Examination shows very little. In a few there is evidence of dilatation, but in the great majority of cases you can find very little in the way of an actual objective sign.

There has been a great deal of discussion as to the cause of this condition. No doubt nervous strain plays a tremendous part. Physical strain did not seem to be a contributing factor. Perhaps a good deal of it might be attributed to tobacco. Smoking is almost constant, and nearly always cigarettes. The average runs from 20-40 a day. It is a serious question in the hospitals, where tobacco is issued as food is issued. It is a very difficult matter to cut down tobacco when it is being constantly served. If one goes into the history carefully, one is impressed by the number who have a susceptibility to tobacco. Some men regard smoking as the prime factor in these disturbances of the heart.

Of course, we looked for internal secretion disturbances, but they are nearly always conspicuous by their absence. A certain amount of infection may have played a part, but this is by no means invariable. In a few cases there had been damage to the heart beforehand, but there was no one thing that stood out. The more you observe them, the more you feel the tremendous importance of the nervous disturbance.

Of peculiar interest were the patients with gas poisoning. Early in the summer we got quite a number of gassed patients with what was designated as the "new gas." It was entirely different from any used before. A little later men spoke of it as "mustard gas." I asked many of them what they had noticed. Some had not noticed anything, but others said there was a smell of garlic. A few days later a chap came in who had been a chemist, and he said he was certain the smell was that of arsenic fumes. The men came in with varying symptoms. We had ten men come in together, who had been gassed at the same time with very different results. As a rule they felt nothing at the time. Sometimes there was constriction and difficulty in breathing, but the majority did not know they had been gassed. Some time afterwards, in from 2-3 hours to 2 days' time, the first symptoms appear, a profuse vomiting which lasts a few hours in some cases, in others for days. Many had irritation of the eyes, conjunctival redness and swelling, marked photophobia and inability to use the eyes in a light at all bright. That lasts a varying time, sometimes as long as 2-3 weeks. A few had corneal ulcer. In certain others, the brunt of the injury fell on the larynx. There were some very acute cases of laryngitis, with a good deal of cough, and in some patients marked bronchitis. Perhaps the most curious sign of all was the effect on the skin in certain of these patients. Some of them looked as if they had been stripped and some one had thrown mud on them in the center of the chest, and from there it had splashed all over them. There was nearly always pigmentation and of a remarkable appearance. Some desquamated very promptly, while others went on to an acute dermatitis. The Tommies called these lesions "gas burns." They began as a small bleb, which perhaps might increase until it was as large as the palm of one's hand. I saw no instance in which a soldier was apparently permanently damaged by this particular gas, although it is of course too early to say positively, except in some of the laryngeal cases. The eye conditions recovered perfectly. Some



of the men developed severe attacks of abdominal pain 2-3 weeks after being gassed, suggesting acute appendicitis. The first one I saw had rigidity, muscle spasm and great tenderness and it was a question whether he should be operated upon or not. However, the leucocytes were not increased and we waited; in 24 hours the pain had gone. There were a number of such cases.

The neurological side of the work is a subject upon which you might talk at great length. The two main problems are the injuries of the nervous system and the so-called war shock. Wounds of the head and nerves are simply bewildering. One of the great problems is as to when one should operate and when they should be left alone. Theoretically it may sound easy to decide, but it is a very difficult problem to settle. Among the patients with war shock some will talk frankly about what happened, some have no recollection at all, while others hesitate and you cannot get them to speak. It seems to me probable that in some of these shock cases there has been a certain amount of organic damage. One thing that harms the war-shock patients particularly is travel. A thunderstorm would excite them greatly. With lightning, they would often jump off the bed. If you could let one war-shock patient see another chap "acting up," he would usually subside and quiet down for an hour or two. We did not get a large number of these patients, but when a lot came in, we would generally try to pick out the most intelligent and work the matter out with him. In a certain number of cases, one got marked results. One patient lost all outward signs in about four days. This created a tremendous interest in the ward. We put him to work with other patients and he was the means of clearing up a number of the men who had come with him. When his condition had been explained to him, he said: "Why didn't I know that before? I see the whole thing now. If I had known before I went up to the front, I would never have been like this. I went up and heard a whole lot about shell shock and was all ready for it before it came." This particular man had been buried for a few minutes and came out with well-marked shock. With some cases it was impossible to do anything by analysis or suggestion. They have to have a certain amount of intelligence before one can do a great deal.

Mixed up with the whole subject of gas poisoning is aphonia. Many patients have difficulty with speech and a certain number are definitely hysterical, but I am not referring to them at present. Many patients who had been gassed, or who had had various disturbances, were left with aphonia. The majority improve slowly. Another thing which is extremely common is stammering. A great many of the men stammer, not necessarily the patients with war shock. It is striking to see how many in the wards are affected.

I mention one point because it is appearing quite often in the literature, and that is the cases with foreign bodies in the lungs. I am not speaking of the patients who need surgical treatment, but of those who have recovered and who have foreign bodies in the lungs. As you know, the French surgeons are strongly advocating operating on these patients. One

hears that the mortality is rather high. The feeling in the Canadian service is strongly against operation. I saw a number and in the great majority you could find little in the way of signs. It seems bad practice to meddle with a condition which is not serious, at any rate at present, unless there are definite indications that one is going to make things better.

With regard to tuberculosis in the soldier, my feeling is that you cannot keep the standards up too high. To say as some men have said and written, that because a patient has had tuberculosis and has recovered is no reason why he should be rejected, seems to me to be absolutely wrong; and to say that men with pulmonary lesions that are not causing symptoms should be passed, appears to me to be abject nonsense. The man who has had tuberculosis should not be sent to the front line, although such men could be used back of the lines in many ways. Some writers claim that men with tuberculosis have done very well; perhaps they do, but when you think of them being constantly damp, sleeping in dugouts crowded as closely as possible, and often crowded into cellars, the conditions are certainly bad. In addition, the men with bacteria in the sputum are spreading infection; it could not be otherwise. My feeling is that the men who have had bronchitis or chronic emphysema should not go to the front lines. I do not believe that they should be passed as Class A men.

The medical officers who go to the front have some nice work ahead of them in diagnosing tuberculosis in the soldier. It is an entirely different matter from diagnosing tuberculosis in the civilian. The men have nearly all had bronchitis; they have nearly all lost weight. You hear that every one gains weight at the front; some do, but many have lost a great deal. With the bronchitis, they often have blood-streaked sputum, and there is also often slight fever. You get a man like that, particularly with signs of an old lesion at one apex, and what are you going to do about it? Many men with acute tuberculosis came back from the trenches with no fever, while the bronchitis patients did have fever. The X-ray plates did not help very much, because many patients showed marked shadows through the lungs. Then, again, you have not unlimited time to settle the matter; you have got to decide it promptly. As one senior medical officer said: "What we want in the men in charge is that they make decisions promptly. The man who handicaps us is the man who hesitates in making decisions." Now, how are you going to settle promptly cases like those I have mentioned? If the patient has tuberculosis, he ought to be sent home promptly; but we do not want to send back a chap who has a bronchitis that is going to clear up. The diagnosis of tuberculosis is one of the most difficult problems they have over there.

Another class of diseases is the gonorrheal infections and lues. The work in a war hospital gave me a big surprise in reference to them. There are more patients with lues in the medical service of hospitals in this country to-day, several times over, than in the general military hospital. Cases of active infection would not be seen in general hospitals. However, when one takes a 1000 bed service constantly full, one would expect a

considerable incidence. The only gonococcus cases were old infections and there were very few of those. Instances of lues were extremely rare. We always had a large number of Wassermann reactions done, and the amazing thing was to find how few were positive. Diagnoses made by the Wassermann were very occasional; indeed, there was nothing like the occurrence that one gets in an ordinary civil hospital. A certain number of the men had been most efficiently treated and showed negative reactions. The army treatment for lues is very thorough.

Just a note about the dental work. That was a very pleasant surprise. There are not many hospitals in this country to-day that are having anything like the grade of dental work done that was carried on in the military hospital to which I was attached. The whole staff was there all the time and any doubtful cases went to the chief at once. The mouth condition in the soldiers was much better than one would expect it to be. The men were taught to take care of their mouths, and it was a pleasure to see the way in which the dental work was done.

Mention should be made of the orthopedic work. American orthopedic men are largely responsible for the establishment of orthopedic centers attached to different hospitals. One cannot speak too highly of the work they are doing.

The X-ray work is a tremendous burden. The regulation is that any patient who may have a foreign body in him must be X-rayed, and with one or two hundred coming in at once, you may imagine the strain.

The mortality in the hospitals in England is surprisingly low. On the medical service where I was during the summer, there were four deaths, three from tuberculosis and one from pneumonia. There were no deaths from nephritis and none from gas poisoning. The deaths on the surgical side were also very few.

One point that comes up constantly is that of prognosis and this is most difficult to handle. Here is a man who comes in, and the question arises, "Is he likely to be well in a month, or will it take three or six months, and at the end of that time what sort of shape will he be in?" That problem comes up every day. With the Canadians, if the case was to be a long one, it was better to send him back to Canada. If he is going to get well, of how much use will he be? The problems are very much the same as those the American troops will have; and one must decide promptly as there are always patients waiting to come in. Another point is that it is so difficult to get experience. You discharge a man and send him on to a convalescent home and then you see no more of him. You cannot easily get data concerning him. Deciding wisely about the outlook for a patient is perhaps the most difficult problem of all.

The personal side is most interesting; it was a pleasure to spend as many hours as possible in the late afternoon and evening talking to the men. You could not get such a varied collection of men anywhere else. I often think of three adjacent beds in one of the wards. In one was a Montreal barrister, a graduate of an English university, in the next a

typical Devonshire rustic, and in the third a Canadian Indian. It was impossible to get the men to talk much about what they had done, and not much about what they had seen. One of the most interesting groups came in one night, and just by chance about 20 beds in one ward were filled by men who had gone to France in August, 1914. When you saw those men you realized to some extent why that original force was able to do what it did. It was the first time that one or two of them had been back in three years. You could not get them to talk very much. They had, of course, been through all the terrible first days of the war. The thing that came out in talking with them was the fearful fatigue. As one chap put it: "You would get a chance to stop and you would drop there and feel that you could never get on your feet again. The whole thing now is just a blur of fatigue, beyond anything anybody could describe." Those were the chaps one felt like saluting for what they had done for every one of us.

They are great readers and devour books. What impressed me most was the amount of serious reading many of them were doing; collections of poems from many authors were extremely popular. It was surprising to find how much Shakespeare was read. Of course, they were not particularly keen on war literature.

The men are great collectors. One night when a convoy was coming in late, I saw the stretcher bearers having a hard time of it with one chap who had what appeared to be a considerable mass projecting on either side of the stretcher. The weight was so great they were obliged to put the stretcher down to rest. Across the foot was a great sack about 6 feet long, full at first sight of what appeared to be junk. The chap had collected helmets and all sorts of stuff. The wonder was how he ever got it through.

The personal side of the work was intensely interesting. The gratitude they had for what you were doing for them made you ashamed; it seemed so little compared with what they had done.

One important thing I would like to emphasize for the medical men who are going over. The first lesson a soldier learns is that of obedience and the second is how to wait. That lesson we all must learn. You cannot expect that the wounded and sick are going to come in at maximum all the time, although you have got to be prepared for the maximum. The medical organization has to be prepared for the largest possible volume of sick and wounded that can come at any given time. You can only do that by having many more men than are necessary for the average. Of course, the waiting is slow work, but it is one of the things that has to be learned.

The thing that made the strongest impression on me over there was the spirit of the men. I did not see the men at the front, but of the men in the hospitals nothing finer than the patience shown can be imagined. I cannot think of any one working in a war hospital for even a short time without coming away with his belief in the essential soundness of human nature strengthened.

NOVEMBER 19, 1917

1. **Studies on Blood Sugar.** DR. LOUIS HAMMAN and DR. I. HIRSCHMAN.
2. **Blood Cultures in Miliary Tuberculosis.** DR. MILDRED CLOUGH.  
Published in the BULLETIN, December, 1917.
3. **Auscultation of the Pulmonary Apices in Young Men.<sup>1</sup>**  
(Abstract.) DR. JOHN T. KING, JR., First Lieut., M. R. C.

The observations reported here were made during a recent examination for tuberculosis of about 22,000 troops at Chickamauga Park by a board of tuberculosis examiners. During the course of the work numerous men were found to present certain crackling sounds during auscultation, especially in the super-clavicular fossæ, which so closely simulated râles, that their identification became the most difficult problem that had to be solved. It was of importance to identify such sounds, because the board was authorized to disqualify any soldier who showed persistent moist râles in the upper lobes. During the latter part of the work the writer noted the frequency of adventitious sounds in the upper lobes in the examination of 819 men.

In 4 per cent of men examined crepitations were heard at or near one or more joints: the joints especially noted were the scapular, costo-sternal, and sterno-clavicular articulations and the shoulders anteriorly.

In 2.8 per cent certain crackles, usually rather loud and explosive, were heard for one or more respirations at the apices, disappearing promptly during continued breathing.

In 2.07 per cent were found the persistent apical clicks or crackles of the type that had proved so confusing.

No description of the last-named group of adventitious sounds was found in the usual text-books on thoracic diagnosis. Bushnell refers to a brief description of such crackles noted by Rosenbach over 40 years ago. He found them most often in muscular young men and children.

Joint crepitations may often be recognized by their groaning or grating quality. Confusing scapular sounds may be eliminated by one of three procedures: (1) By having the subject fold his arms and grasp the opposite shoulders with his hands; (2) by having him, while standing, bend the trunk forward to a horizontal position and allow the arms to hang limply downward; (3) by having him grasp an object at a level about as high as he can reach and exert enough weight on his arms to fix the scapulae apart. Crepitations from the lateral sternal articulations may often be eliminated by having the subject throw his shoulders as far backward as possible.

Transient apical crackles, originating probably in the neck muscles, are often easily recognized by a loud, explosive quality. They are seldom reproduced by coughing.

The persistent apical crackles in healthy men are more difficult to distinguish from true râles than are any other adventitious sounds in the upper lobes. They are of every size, and occur singly or in sequence. Single clicks are usually of this type. All such crackles are most often heard when the subject holds his head in the position customary during examinations—slightly averted from the apex under examination. Such sounds often disappear if the chin is placed high in the air or if it is turned slightly toward the side that is being examined. These crackles are seldom increased by coughing, and usually occur during inspiration, but may be present in both phases of respiration. They are usually more intense when the stethoscope is directed medially, toward the neck muscles. Rosenbach reproduced such sounds by moving the neck muscles while the subject held his breath. Apical crackles of the above types almost certainly originate in the neck muscles and are of significance only in being differentiated from intrapulmonary râles.

NOVEMBER 23, 1917

On Two Fronts. DR. WILLIAM T. GREENFULL.

<sup>1</sup> Published in *The Military Surgeon*, January, 1918.

## BOOKS RECEIVED

*A Treatise on Regional Surgery.* By Various Authors. Edited by John Fairbairn Binnie, A. M., C. M., F. A. C. S. Vol. I. With 351 illustrations. 1917. 8°. 652 pages. P. Blakiston's Son & Co., Philadelphia.

*Saint Bartholomew's Hospital Reports.* Edited by F. W. Andrews, W. McAdam Eccles, G. E. Gask, W. D. Harmer, H. Thursfield, H. Williamson. Volumes L and LII, 1914 and 1916. 8°. 244 pages, 167 pages. Smith, Elder & Co.; John Murray, London.

*Obstetrics.* A Text-book for the Use of Students and Practitioners. By J. Whitridge Williams. Fourth enlarged and revised edition. 1917. 8°. 1029 pages. D. Appleton & Co., New York and London.

*Carnegie Endowment for International Peace.* Founded December 14, 1910. Year Book for 1917. No. 6. 1917. 8°. 213 pages. Washington, D. C.

*The Rockefeller Foundation, International Health Board.* Third Annual Report, January 1, 1916–December 31, 1916. 1917. 8°. 246 pages. New York City.

*State of Iowa, Board of Control of State Institutions.* Tenth Biennial Report for the period ending June 30, 1916. [1917.] 8°. 405 pages. Des Moines, Iowa.

*Surgical Therapeutics and Operative Technique.* By E. Doyen. English edition prepared by the author in collaboration with H. Spencer-Browne, M. B. Cantab., etc. Vol. I. 1917. 8°. 746 pages. William Wood & Co., New York.



# BULLETIN

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### CINQ ANS APRÈS<sup>1</sup>

By F. C. SHATTUCK, M. D., Boston, Mass.

Many a man has wished he might return to earth and note the changes since his demise. I have never been of that number, for is it not an endless chain? One return might merely whet the appetite for another, stimulating desire, the extinguishment of which, so the Buddhists hold, should be our one and constant aim. Or, what seems more likely, the return tripper might find himself hopelessly out of place, thoroughly wretched. Probably the existing plan is best. It would seem wise to accept it as such, inasmuch as we have no choice.

Absolutely without volition of my own, and without blame attaching to the all-highest Kaiser, if any credence can be given to his unwonted burst of modesty when he told us he did not will this war, I have been resurrected, and vouchsafed a glimpse of what five years can do in hospital medicine. The Kaiser has done his best to convince his people that nothing in the heavens above, in the earth beneath, or in the waters under the earth, takes place contrary to his will. I see it stated that he has been graciously pleased to ennoble God, who is henceforth entitled to enjoy the prefix von—von Gott.

In the spring of 1912, having reached the age limit then in force at the Massachusetts General Hospital, I was consigned to the tomb, and, indeed, was such a horrible example of dry rot—or something—that the age limit was promptly put down from 65 to 60. May I add that I think this a wise step, promotive of far more good than harm? The ancient adage says “a young man for action, an old man for counsel.” A service in a modern hospital is surely a sphere of *action*, and an old man’s counsel can always be had if wanted. It is well for those who are growing or have grown old, to read, from time to time, mark, learn, and inwardly digest, Kipling’s poem on the old men, as salutary as some of it may be brutal.

The war came; then our entrance into it, and the depletion of hospital staffs for the United States service. Shorthandedness became acute, and it was deemed necessary to rob something, so the authorities at the Massachusetts General Hospital began by robbing the grave, holding the cradle in reserve for the present, and after five years of desuetude, I trust relatively innocuous, I found myself again in charge of a medical service in a hospital. Some of the changes I note after this interval, and some reflections thereupon form the subject of my short and informal talk to you this evening.

<sup>1</sup> Read before a meeting of The Johns Hopkins Hospital Medical Society, January 21, 1918.

One striking fact was the small number of typhoid cases. I think the number was diminishing while I was still active; but I could not help contrasting 5 per cent of medical beds occupied by typhoid patients with nearly 50 per cent as I have seen in Octobers of the past. Two of the cases in my service convey a lesson. They were a brother and an uncle of an Italian who was in the hospital in the summer with typhoid, but carried a bacilluria six weeks after recovery in other respects. He was reported to the Board of Health and by them put in another hospital where he stayed two weeks, then being discharged, as reported, with constant negative cultures. He went back and roomed with his brother and uncle, both of whom came down with typhoid. The original case re-entered the Massachusetts General Hospital and gave a positive culture. I had supposed hexamethylenamine to be truly specific for typhoid bacilluria, and, at the time of the Spanish war, I ordered the drug given as a routine thing to every case of typhoid. It seems, thus, that a few cases are resistant. The spread of typhoid through the urine of a carrier would seem a more insidious danger than through the feces, a more offensive excretion. The time seems near when it will be as hard to demonstrate a case of typhoid to students as it is now a case of smallpox. I was gratified to find that the liberal diet in typhoid, of which I was an early advocate, is still in force. What plan of diet you follow here I do not know, but McCrae in 1907 either had never heard of a liberal diet in typhoid or perhaps thought it too dangerous even to mention.

Peptic ulcer is my next theme. I was formerly quite accustomed to the nearly constant presence in my female ward of several cases of gastric ulcer, almost invariably with the clinching evidence of hemorrhage. These almost always did well under purely medical treatment unless there was distinct pyloric stenosis. I now find a decidedly larger number of cases in the male ward, often sent in for such study as the slender purse cannot afford outside of the hospital. The X-ray here occupies a more prominent position than it did, partly through improvements in methods, mainly through accumulated experience. Our X-ray expert, Dr. Holmes, holds the, to my thinking, sound view that X-ray evidence of ulceration in or about the upper digestive tract is corroborative rather than determinant. Its positive value is great when it fits in with evidence derived from the history, physical examination and other tests. Am I warranted in suspecting that some X-ray experts attach undue finality to their findings? Personally, when the X-ray and the other evidence diverge, I should put the X-ray in the second place. Let me mention two cases, among others, which come into my mind in which X-ray evidence would have been helpful. A young woman, not a bleeder either of congenital or any apparent acquired origin, had persistent hæmatemesis. I urged operation, which showed that the blood oozed from the whole gastric mucous membrane. Possibly an X-ray might have saved her from operation and from death.

A middle-aged woman was transferred from the surgical to my ward as inoperable. She had coffee-ground vomit, no free HCl and an epigastric tumor. We all concurred in the diag-

nosis of gastric cancer, and her friends were advised to take her home as speedily as possible to a neighboring state. Later I was told that she died of pneumonia several years after discharge from the hospital, and that an autopsy showed her epigastric tumor to be a displaced kidney.

Peptic ulcer still seems to me to belong to the physician with the surgeon in reserve. There can be no question as to the addition to our power of recognition of peptic ulcer afforded by the ante-mortem knife of the surgeon. You all remember Dr. Wendell Holmes' comparison of an autopsy to inspection of the fire-works the morning after the Fourth of July. Modern surgery has amplified our knowledge of the pathology of the living as nothing else could have done. At one time, 10 years ago, if you will, with the best intentions to keep an open mind, I felt that indiscriminate gastroduodenal surgery was in the ascendant, that surgery was too often regarded as a short cut to cure. I could not satisfy myself how gastroenterostomy could obviate the underlying cause of ulceration. Marked more or less temporary improvement might be accounted for by the rest which operation brought the patient and his stomach.

I recall the case of an unfortunate young woman in my service who had undergone at least two operations for dyspepsia in another hospital. She was ungrateful enough to be no better, and entered to find out whether another operation might restore the upper digestive channels as planned by the Divine Architect. Adhesions were separated, and the gastroenterostomy closed—with considerable relief up to the time of her discharge. It has been impossible to learn of the end result.

This year I got the impression that the surgical treatment of peptic ulcer is more discriminating than it was. My time and basis for judgment were too limited for more than an impression; but I can see no reason to change the conservative view I have long held on this point. The crucial test of time and the growth of "end result" statistics should put us in a better position to judge than was occupied five years ago. We are less patient than we used to be. We are in a hurry to "get results." And a clean surgeon rarely kills.

Am I dreaming when I think I recall that recognized cases of gastric ulcer were rare in the wards of this hospital 25 years ago? Tell me, Dr. Thayer.

Five years ago, with us at the Massachusetts General Hospital, at least, the fresh, cold air treatment of pneumonia was in full swing. A head-high screen around the bed of the pneumonic did something to temper the air from the open window to the other shorn lambs in the ward. In short, the open-air treatment was carried out as far as practicable in an open ward. This autumn the screen was still in evidence, the open window less so, as it seemed to me. Why then the screen?—I asked myself. The ordinary pneumonias are not easily contagious, and a patient who is either a menace or a real disturbance to others should not be in an open ward. Though asphyxia is rarely a potent factor in pneumonic death, I have long held, and used to teach that a plentiful supply of fresh air was desirable. The young and vigorous will stand, and possibly benefit by, a lower temperature than the old and feeble. The craving

of old people for warmth would seem to indicate an intolerance of cold, due in part, at least, to lessened activity or involution of the thyroid gland. Five years ago the studies of Cole and others on the varieties of the pneumococcus had not progressed far enough to help in prognosis or treatment. The routine effort to determine the type of pneumonia I noted as another innovation. Until some efficacious antidotal treatment for pneumonia is discovered, the mortality will remain about the same. Here may I express my great sympathy to you in the loss of Theodore Janeway? In his case surely death loved a shining mark.

A paper by Dr. Charles H. Lawrence and myself will appear shortly, analyzing the pneumonias at the Massachusetts General Hospital from 1889 to 1916, about 3500 in number. Our data begin where Townsend and Coolidge left off, and we find the mortality practically the same in the days of heroic, expectant and alcoholic, symptomatic, and fresh air treatment. I wonder whether the pendulum has not swung too far away from alcohol in cases of profound general sepsis. Many of us elders who have lived through the unquestioned abuse of alcohol in disease cannot get rid of the belief that there are cases of sepsis in which alcohol, even in massive doses, are life-saving, if given with brains. I emphasize brains, for the best results are to be obtained only under close and skilled observation. All trace of alcohol in the breath should disappear before more is given; so, also, any toxic effect, flushing, for instance. Fifty years from now will alcohol be considered always, everywhere, under all circumstances, the unmitigated poison which some present day apostles hold it to be; and which the American Medical Association has pronounced it to be? Fully realizing that what I may think cuts no ice, to use a colloquialism, I doubt. Mercury and bleeding were so abused that they fell into disuse, but have come back. I find that in 1912 in the Massachusetts Hospital \$551.17 was spent for alcohol as an internal remedy against \$133.36 in 1917. The whiskey bill in 1917 was 20 per cent larger than in 1912, but this probably indicates a rise in the price, not an increase in the amount. The following table may prove of interest:

	1908	1912	1917
Ale .....	\$ 94.75	\$174.97	\$50.95
Beer .....	67.46	31.50	6.24
Brandy .....	114.75	131.62	....
Champagne .....	77.90	57.75	16.00
Wines .....	203.08	114.83	11.13
Whiskey .....	....	40.50	49.04
.....		\$551.17	\$133.36

The value of the X-ray in the detection of gall-stones has certainly increased in the past five years. This gain I am told is due to a shortening of the time of exposure from 20 seconds to a fraction of a second, thus reducing mobility of surrounding parts as a source of error.

To turn now from special diseases to the general trend of thought and practice in the past five years. I see real progress in the care and thoroughness with which the sick are studied, their histories and the course of their maladies recorded. In-

deed, I found the records so voluminous and minute that it was hard to see the wood by reason of the trees. The labor of the chief of staff would be lightened and the mental training of the younger men promoted, as it seemed to me, by the addition of a brief, clear, logical, consecutive statement of the essentials of each case, especially the complicated ones. The power of terse statement with a quick eye for perspective and values is worth the labor of attainment. Are dictation and the typewriter enemies of prolixity and slovenliness in the use of our wonderful language? As an intimate knowledge of King James' Bible wanes, English decays.

As I look back 50 years when I began to frequent hospitals seriously, I note a wonderful advance in diagnostic and therapeutic procedure. The major part of this, certainly in importance, dates from the birth of bacteriology; chemistry, and some knowledge of the hitherto unknown vibrations, the X-rays among others, are also vital factors. When I began the study of medicine and for years thereafter we soon came to an end of our means of investigating disease as exemplified in a patient, and could devote much of our energies to caring for the sick man, a human being different from any other upon earth, and meriting study as a sick man, not merely as a case of disease. With the multiplication of instruments of precision, of chemical and other tests, psychological included, with the steady improvement in X-ray technique, the possibilities of study have grown many fold. The pace has not slackened these past five years, and some patients surely now have time to die or get well before a really scientific diagnosis is reached, and there is a greater chance for the patient to be forgotten in his disease. There is a possibility of error both in observation and in interpretation. This tendency, if it exists outside of my imagination, is enhanced by the polyglot publicum of our wards. The wall of language impedes some of the currents of human medicine. Some years ago I had a census made in my ward with 22 patients. There was only one I should call a Yankee, that term connoting to me a person of relatively pure New England blood. With many of these patients we can communicate only through an interpreter, not always at hand. Human fallibility constantly lurks behind even the instrument of precision and the chemical test.

I well remember an observation dropped by the shrewd and kindly, old, as he seemed to me then, Dr. Tessier of the Lyons Hôtel Dieu, 40 years ago—"Le médecin guérit rarement, améliore souvent, console toujours." To-day he cures oftener than he did then, for he knows far better what things are curable and how they are to be cured. He also relieves oftener. Does he as invariably and as surely console? There are still all too many cases in which consolation alone remains.

While I rejoice in and try to do justice to scientific progress, I should be sorry to think that any real values shrink or vanish. To slightly paraphrase a saying of our Lord—"Thus ought we to do but not to leave the other undone." I believe in the perfectibility of man—in time. It is surely in place—is it not?—to enter a plea for humanism on the scene where a great humanist scored so many of his triumphs, your and our William Osler.



## DISCUSSION

DR. W. S. THAYER (Abstract).—It was my rare good fortune nearly 30 years ago to come into my first service in the Massachusetts General Hospital under Dr. Shattuck, and it has been deeply interesting to me to hear what he had to say. He has mentioned various things that have interested me particularly.

In the first place, his observations on gastric ulcer. It is true that in 1890 when I first came here, for several years we had curiously few obvious gastric ulcers; whereas during the service of three months I had under Dr. Shattuck, we had a number of outspoken cases of these ulcers. Although we had few cases then, we have made up for it since. I think it was simply one of those remarkable periods during which we had a few cases come to us.

I was very much interested in what Dr. Shattuck had to say about sepsis. I confess to feeling very much as he does. I cannot believe that I have been absolutely deceived in the value of alcohol in some acute infections. When I was in the Massachusetts General, we were using alcohol quite freely. I remember one particular patient with pneumonia who was taking 36 oz. of whiskey a day. I was called up one night about midnight by the nurse, who said she was afraid something serious had happened. I hastened to the ward and found an individual with a perfectly normal temperature, sitting on the side of his bed and singing in the most ribald fashion. He had had his crisis and the alcohol was being continued! I should not be surprised if in after years we do not perhaps use a little more alcohol in acute infections than we are employing to-day.

It was nearly 30 years ago in the fall of 1888, when I came into the Massachusetts General and began my service with Dr. Shattuck. It was a most interesting and valuable service I had during that year. He was a good deal the sort of doctor that

he has described to-night, if you read through what he said. He was not only a very acute clinician and a remarkably good observer, but he taught us how to treat patients in every sense of the word. I never have seen one who was more able to stimulate and encourage his patients and who failed less in doing so. Dr. Shattuck not only taught us to observe, but he taught us what no one else at that time was teaching in the Massachusetts General Hospital, and that was how to record our observations. He made exceedingly careful bedside notes. They were sometimes long for us to write as house officers, but they were exceedingly valuable when written down. He taught us something more, which was perhaps as valuable as anything else, and that was to love him.

DR. WELCH.—Just a word about Dr. Shattuck. His remarks bring back to me a good deal that used to be written in the Roman histories of my early days about succeeding consulships. That is a very good idea, and I do not know but that it might be adopted as a regular thing. A man retires from his consulship, is succeeded by somebody else and some five years later he makes a review which does not necessarily represent progress, but represents what changes resulted from a change in consulship. That is what interests me particularly about Dr. Shattuck's observations. I hope he will have the same opportunity to give us another five years' review. It would certainly be worth hearing.

Dr. Shattuck does represent, as Dr. Thayer has said, the very best type of doctor, combining the scientific and the practical, the interest in the case and the interest in the patient. No amount of scientific work will in itself alone make a great clinician. The great clinician must be a combination of that scientific interest and that practical quality, which can be acquired, although not always readily, which looks upon the patient not as material, not as a case, but as a human being.

## DIABETES: THE RESULTS OF PAST TREATMENT AND FUTURE PROBLEMS<sup>1</sup>

By ELLIOTT P. JOSLIN, M. D., Boston, Mass.

At the beginning of 1914, the outlook for diabetic patients was depressing. The statistics of the Massachusetts General Hospital showed that in the preceding 16 years for each 100 diabetes admitted 28 were discharged dead, a record which duplicated the experience of the hospital between 1824 and 1898. Physicians dreaded to place their patients in an institution lest the treatment there prescribed prove more disastrous than that adopted by the patient's fancy. Surgeons dodged the diabetic, while the obstetrician was out and out afraid of diabetes and urged pregnant women to have abortions. The neurologist, dermatologist and ophthalmologist would throw up their hands at complications within their respective spheres and exclaim, "Cure the diabetes and then we will help the patient." It is hard to realize that these conditions prevailed only four brief years ago.

As so often happens when the clouds are darkest, light unexpectedly appears, and I recognized its approach one afternoon while talking with Dr. Allen. It happened in this way: We were discussing one of my severest cases (Case No. 344) and I pointed out how the type of diabetes in this instance changed from severe to mild as tuberculosis came on and the

patient progressively became weaker and lost weight. I remember telling Dr. Allen that if he could explain why this change took place the problem of diabetic treatment would be greatly advanced. The next day I heard from him that he felt he could explain the reason for the improvement, and furthermore believed that he would be able to demonstrate the cause for it by animals, and soon after I was gratified to learn how doctors could give their diabetic patients renewed hope. You are familiar with his experiments by which he showed that dogs made artificially diabetic and then forced progressively to lose weight gained in tolerance for carbohydrate.

The far-reaching results of these experiments immediately began to show, and are illustrated by the following table:

TABLE I  
THE RECENT IMPROVEMENT IN DIABETES AS SHOWN BY THE STATISTICS OF THE MASSACHUSETTS GENERAL HOSPITAL

Period	Monthly during hospital stay		
	No. of cases	No. of deaths	Percentage
1824-1898	172	47	27
1898-1914	281	80	28
1914	51	8	16
1915	89	11	12
1916	103	8	8
1917	105	6	6

<sup>1</sup> Presented before The Johns Hopkins Medical Society, February 4, 1918.

Your attention is directed to the stationary character of hospital diabetic mortality for 90 years and its abrupt and steady diminution following Dr. Allen's announcement. A reduction of mortality from 27 per cent to 6 per cent would appear to be sufficient proof of improvement, but other evidence is available. At the New England Deaconess and Corey Hill Hospitals there were under my care during 1917, 181 diabetic patients. Of these four died, a mortality of 2 per cent, and I believe that this year three of these patients could be saved. I have summarized my personal statistics in Table 2.

TABLE 2

AUTHOR'S STATISTICS OF DIABETIC PATIENTS TREATED AT THE NEW ENGLAND DEACONESS AND COREY HILL HOSPITALS

Year	No. of cases	Mortality during hospital stay	
		No. of deaths	Per cent
1913	43	4	9
1914	60	3	5
1915	109	6	6
1916	164	8	5
1917	181	4	2

What other disease, chronic or acute, can show a similar reduction in mortality during these last four years? After all, diabetes has points in its favor. Never forget that unlike cancer and rheumatism, it is painless; unlike tuberculosis, it is clean and not contagious, and in contrast to many diseases of the skin, it is not unsightly. Moreover, it is susceptible to treatment and the downward course of a patient can usually be promptly checked. It is true that treatment is by diet and not by drugs, but the patients who know the most, conditions being equal, can live the longest. There is no disease in which an understanding by the patient of the methods of treatment avails as much. Brains count, though knowledge alone will not save the diabetic. This is a disease which tests the character of the patient, and for successfully withstanding it, in addition to wisdom, it demands of the individual honesty, self-control and courage.

This striking improvement in diabetic treatment belongs to the first year of the disease, the year which I call the diabetic's danger zone. This is important, for it is the most useful year to the diabetic and to the community. The first year of the disease is pre-eminently the year of coma. Eighty-seven per cent of all diabetics who have come under my care and have later died during the first year of the disease have succumbed to it. And yet to-day everyone will agree that diabetic coma during the first year of the disease should be considered an accident which can and should be avoided not only in adults but in the youngest child.

How much the average length of life of the individual patient has been increased by our recent methods no one knows, but the following table gives my own personal experience, ending December 1, 1916. Eventually I hope to bring this table up to January 1, 1918, and to continue it still further. As it stands now the average length of life of my fatal cases for the different decades is considerably under the average length of life of the living cases. This is a hopeful sign.

TABLE 3<sup>2</sup>

DURATION OF LIFE OF FATAL AND LIVING CASES OF DIABETES, DECEMBER 1, 1916

Age at onset years	Fatal		Living	
	No. cases	Average duration	No. cases	Average duration
0-10	37	1.3	22	2.6
11-20	55	2.8	40	2.9
21-30	51	3.1	61	5.3
31-40	64	4.4	94	7.2
41-50	95	6.4	184	7.3
51-60	115	6.9	163	6.3
61-70	67	5.7	63	6.1
71-80	16	3.6	12	5.3
81-90	..	...	1	1.3

The prolongation of life holds quite as strongly with the young as with the old. It was rare formerly for a patient in the first decade of life to live more than a few months. Now the children are expected to live at least twice as long. This may not mean much in itself, but it does in the treatment of diabetes as a whole, and it demonstrates that if the duration of the disease in the severest cases has been doubled by the improved methods of treatment, marked gains in treatment ought to follow in the mild types. With the middle-aged I have been able to collect from my records 33 cases who have not only lived long, but have exceeded their theoretical expectation of life at the onset of their diabetes. Moreover, nearly a year ago Horner and I<sup>3</sup> found that 5 per cent of the cases had lived over 15 years.

Mention was made of the surgeon's and obstetrician's avoidance of the diabetic patient in 1914. To-day I can testify from my own experience that without fear and with success surgeons remove the appendix, uterus, ovaries, prostate, gall-stones; resect cancers of the bladder or large areas of intestine on account of strangulation, and even operate on the lung. The obstetrician now carries his patients through labor without danger and there are a good many healthy children living to-day whose lives are a witness of improved diabetic methods. Neuritis and affections of the skin are rare exceptions. On January 26, 1918, Case No. 817, whose carbuncles were so extensive three years ago that the attending physician felt it was kindness to allow him to die, came into my office at the age of 76 years, having gained 59 pounds since I first saw him! I confess that it is not often that the diabetic of so many years' duration complains as did he of growing fat.

Improvement is also registered by successively severer and severer cases being rescued from coma. Six months ago I was able to publish a list of 15 severe cases of diabetes recovering from acidosis, with subsequent discharge from the hospital, without the use of alkalis.<sup>4</sup> Estimating the severity of these cases in terms of carbon dioxide tension of the alveolar air or of the blood, their acidosis was included between the boundaries of

<sup>2</sup> Joslin: *Treatment of Diabetes Mellitus*, 2d Edition, Lea & Febiger, Philadelphia, 1917.

<sup>3</sup> *Am. Journ. Med. Sciences*, 1918, Vol. CLV, p. 47.

<sup>4</sup> Joslin: *Loc. cit.*, Table 172, p. 389.

15 and 25 mm. mercury. Compiling a second series one month ago I was able to substitute seven cases in the original list by seven others still more severe, thus changing the limitations of the carbon dioxide to between 14 and 22. In anticipation of this meeting, I wrote Dr. Geyelin of New York and he has furnished me with cases of his own and at least three of these will replace three of mine, thus enabling a new series of 15 cases to be compiled of threatening coma treated successfully without alkalis, of which, thanks to Dr. Geyelin, the lowest limit, measured in terms of carbon dioxide tension, is reduced to 13.65 mm. mercury in the blood, and the highest limit to 20, measured in terms of carbon dioxide in the alveolar air. These results are shown in Tables 4 and 5.

TABLE 4

TREATMENT DIABETIC COMA SUCCESSFULLY TREATED WITHOUT ALKALIS. THREE GROUPS OF CASES, 15 EACH, COMPILED AT SUCCESSIVE DATES, EACH GROUP SEVERER THAN THE PRECEDING.

Date of compilation	No. cases	Limits of treatment in terms of CO <sub>2</sub> tension in mm. Hg. in blood and alveolar air
September, 1917 .....	15	15-25
January, 1918 .....	15	14-22
February, 1918 .....	15	13.7-21

TABLE 5

SUCCESSFUL TREATMENT WITHOUT ALKALIS OF 15 CASES OF DIABETES THREATENED WITH COMA

Case No.	Date	Level	CO <sub>2</sub> tension in mm. Hg. in blood	Alveolar CO <sub>2</sub> tension in mm. Hg.
691	Nov. 15, 1917...	+	...	20
1200	May 29, 1917...	...	2.3	18
786	June 11, 1916...	++	3.9	18/20
	12	+	3.2	24 21
Dr. Geyelin	May 31, 1917...	+++++	...	13.7 ..
J. G.				
942	July 12, 1916...	+++	4.4	20 20
	13	++	3.7	.. 17
938	Nov. 2, 1917...	+++++	1.3	.. 18
Dr. Geyelin	Apr. 5, 1917...	+++++	...	21
M. S.				
Dr. Geyelin	Oct. 18, 1917...	+++++	...	16
H. J.				
755	Apr. 15, 1917...	+	1.6	.. 18
1011	Mar. 29, 1916...	++	1.8	.. 23
	Apr. 13, 1916...	++	...	.. 22
	Sept. 25, 1917...	+++++	...	.. 15
1085	Oct. 30, 1916...	?	1.7	28 20
1196	Dec. 8, 1916...	...	1.6	.. 21
	9	++	6.0	26 22/14
	10	+++	3.3	.. 18/20
	11	+	3.1	26 20
	12	...	3.3	.. 21
	13	...	2.9	.. 21
1070	June 23, 1916...	...	1.9	21 20
1012	Sept. 13, 1917 ..	+++	...	.. 14
	14	++++	2.5	21.3 14
	15	?	2.3	.. 16
1120	Sept. 6, 1916...	+++	...	.. 21
	7	...	...	.. 18
	Oct. 11, 1916...	++	1.9	.. 22
	14	0	...	.. 20
	27	+	...	.. 15

Individual cases are more striking than convincing. Each month I derive encouragement from the return of an old case. A recent one is Case No. 866, first seen in 1915 at the age of 32 with onset one year before, whose consumption of food prior to admission to the hospital in 1915 was extraordinary even for a diabetic. His regular ration was two dozen eggs, three pounds of meat and 30 apples, with other food unrecorded. The sugar in the urine at this time amounted to 4 per cent. On January 28, 1918, he again returned to the hospital, after an absence of three years, but this time sugar and acid free and with the report of having remained so almost constantly! During the interval he had at no time gone to a physician's office and at no time missed work on account of illness. His present diet and method of living interested me extremely, for it shows what a courageous man can do. It consists of a pound of cabbage at each meal, and for the day two eggs, 60 grams of bacon (weight uncooked), six ounces of meat at dinner and the same for supper, 120 c. c. of 20 per cent cream, and about 60 grams of butter. I do not report this as an ideal diet, but upon it this man has supported his family and lost but six and one-half pounds in weight in three years. Mark this! He retires at 8 p. m. and rises at 6 a. m., 10 hours in bed! The course of this case should be compared with the course of patients who suffer from other chronic diseases. How many nephritic, cardiac, arteriosclerotic or chronic rheumatic patients could touch as low a limit of life as this patient three years ago and regain to such an extent their efficiency?

I do not share the opinion of some hospital clinicians who in the face of cases like this, and in these days when the hospital diabetic mortality has been lowered from 28 to 2 per cent, pretend to be discouraged about the treatment of diabetes and are prone to fill their wards with patients showing interesting electrocardiograms whose efficiency can seldom be regained.

Will the recent improvement in treatment continue? I believe it will, and for three reasons. First of all, the trend of statistics points to it, as is proven by a study of the statistics of the Massachusetts General Hospital. You have undoubtedly observed that the reduction in hospital mortality has taken place gradually. Each year has shown progress, and my own figures illustrate that this improvement can proceed still further. In the second place, the enemies of the diabetic are now more clearly recognized. We know exactly with what we must contend. This is evident from Table 6.

TABLE 6

CAUSES OF DEATH OF 516 DIABETIC PATIENTS SEEN IN PRIVATE PRACTICE ONE OR MORE TIMES FROM 1894 TO DEC. 11, 1916

Coma .....	60 per cent
Cardiorenal .....	13 " "
Infections .....	10 " "
Cancer .....	5 " "
Tuberculosis .....	4 " "
Inanition .....	1 " "
Miscellaneous .....	6 " "

I would particularly direct your attention to the 60 per cent of deaths due to coma and the 1 per cent of deaths due to inanition.



tion. Since fasting treatment, introduced by Dr. Allen, has been adopted, the fear has arisen that inanition would figure prominently as a cause of death of diabetic patients. As yet this has not proven to be the case. Inanition will undoubtedly increase in frequency, but I shall not allow it to divert my attention from the 60 per cent of the cases who die of coma. All but two of my fatal cases in children have died of coma. Of all the diabetics coming under my supervision, 87 per cent of those who have died during the first year of the disease have succumbed to coma, and even 44 per cent as well of those cases who have lived more than 15 years. The one enemy which the diabetic must fight is coma. Thirteen per cent of the patients died of cardiorenal disease, but with modern treatment adapted to impaired kidneys the lives of such patients might be easily prolonged. Infections continue to be a great menace, but are not nearly so serious as formerly, when they were so often complicated by coma. We must expect that the mortality from cancer will rise, and can look for a continued lowering in the mortality from tuberculosis due to the lessened opportunities for contagion. It is better avoided than treated, but even if present does not preclude many years of life.

The third reason for the continued improvement in the treatment lies along several lines. (A) Earlier diagnoses of the disease are being made. By this means, mild cases are discovered and their change into a severer type is delayed or prevented. (B) Coma can be avoided to-day in the overwhelming majority of cases. Whereas formerly numberless diabetics died at the beginning of treatment, to-day such a death excites comment in any well-regulated hospital. Attention has been called to the decrease in coma after surgical operations due to the measures adopted to prevent acid-poisoning and the decreased use of ether as an anesthetic. (C) A new type of ammunition in the battle against diabetes is now being generally adopted. I refer to the education of the doctor, nurse and, most of all, the patient. Whether teacher and student desire to devote increasing time to the study of diabetes, the fact remains that there are four times the number of cases in the United States recognized to-day as in 1890, and thus four times as many to be treated. Instruction in diabetes, therefore, should receive four times the time allotted to it in the curriculum. Diabetes is pre-eminently a disease in which education avails. Fortunately, with the treatment introduced by Dr. Allen, the education both for doctor and patient has been so simplified that the essential facts can be summarized on a small card.

The training of the patient in hygiene, diet and clinical tests constitutes a new era in medicine. Previously tuberculosis was the disease where the education of the patient was most insisted upon and in that hygiene alone was the only subject taught. Many advantages will accrue from the war and not the least of these is the compulsory education of patients and of nurses in matters hitherto supposed to be beyond their ken. To-day I know a group of nurses who specialize in diabetes, and I can trust any one of these nurses to go into a patient's home

and carry out treatment from beginning to end, simply depending upon the family physician for general supervision.

*The Treatment of Diabetes as Practiced To-day.*—The treatment of diabetes as it is actually practiced to-day is very different from what it should be. By no means does it follow the lines advocated at the Rockefeller Institute, The Johns Hopkins Hospital or other large hospitals in the country. I honestly believe that more cases of diabetes are now treated with the diet which appears on the back of a drug firm's advertisement than by any other method. It is still a rarity for a patient to come to me free from sugar and free from acidosis, and the cases are few and far between who have any conception of dietetic values. Diagnoses of diabetes are still made too late. Unfortunate as this is, I am glad to say that I have noted definite signs of improvement, chiefly manifested in the lessened use of drugs. The general practitioner is not to be too sharply criticized, because the methods which are employed in the leading institutions are only of recent origin, and furthermore, the general practitioner has never had a consistent plan for the treatment of diabetes laid out for him. It would be a great mistake if our present simple methods were to be rapidly changed purely for the sake of some slight improvement. When we realize the great advance in the treatment of diabetes which has taken place during the last four years, and at the same time bear in mind the intricate but definite problems which lie ahead, and appreciate the difficulty of interpreting the mass of scientific data just accumulated, we should hesitate long before altering the methods which have brought these gains. In the past, waves of diabetic treatment have followed in rapid succession. From nearly each one of these something has been gained. Let us be sure that we gather the benefit of all the good which is coming in on the present crest before we dive into a new breaker.

*What Should be the Treatment of To-Day?*—In general, authorities agree. The patient should be made sugar-free and this should be done in such a manner as not to produce acid intoxication. The basic principle is fasting, and it makes little difference whether the fasting is absolute or partial. Some of us prefer to omit the fat in the diet before the fast in the hope of warding off acid poisoning, which occurs in a small number of cases following the fast. This method has been most satisfactory in my hands. By this means, along with the prevention of acid poisoning, the patient gets the benefit, without the hardships, of reduced calories. The rules which I follow in the treatment of my cases are very simple, and although I seldom follow these to the letter, for each case is unto itself, I have found the method of treatment so satisfactory that I shall perhaps be more loath to change it than those of you who are just starting in medicine and have not lived through the barren years of diabetic treatment. These schematic rules and the dietetic values necessary for the patient are recorded on this small card, the reading of which may be omitted.

**Preparation for Fasting.** In severe, long-standing, complicated obese and elderly cases, as well as in all cases with acidosis, or in any case if desired, without otherwise changing habits or diet, omit fat after two days omit protein, and then have the carbohydrates daily until the patient is taking only 10 grams; then fast. In other cases begin fasting at once.

**Fasting.** Fast four days, unless earlier sugar-free. Allow water freely, tea, coffee, and thin, clear meat broths as desired.

**Intermittent Fasting.** If glycosuria persists at the end of four days, give 1 gram protein or 0.5 gram carbohydrate per kilogram body weight for two days, and then fast again for three days unless earlier sugar-free. If glycosuria remains, repeat and then fast for one or two days as necessary. If there is still sugar, give protein as before for four days, then fast one, and then gradually increase the periods of feeding, one day each time, until fasting one day each week. I have seen no uncomplicated case fail to get sugar-free by this method.

**Carbohydrate Tolerance.** When the twenty-four-hour urine is free from sugar give 5 or 10 grams carbohydrate (150 to 200 grams of 5 per cent vegetables) and continue to add 5 or 10 grams carbohydrate daily up to 50 grams or more until sugar appears.

**Protein Tolerance.** When the urine has been sugar-free for three days, add about 20 grams protein and thereafter 15 grams protein daily in the form of egg-white, fish or lean meat (chicken) until the patient is receiving 1 gram protein per kilogram body weight or less if the carbohydrate tolerance is zero.

**Fat Tolerance.** Add no fat until the protein reaches 1 gram per kilogram body weight (unless the protein tolerance is below this figure) and the carbohydrate tolerance has been determined, but then add 5 to 25 grams daily according to previous acidosis until the patient ceases to lose weight or receives in the total diet about 30 calories per kilogram body weight.

**Reappearance of sugar.** The return of sugar demands fasting for twenty-four hours, or until sugar-free. Resume the former diet gradually adding fat last in order to maintain as high a carbohydrate tolerance as possible, sacrificing body weight for this purpose.

**Weekly Fast Days.** When the tolerance is less than 20 grams carbohydrate, fasting should be practiced one day in seven; when the tolerance is over 20 grams carbohydrate cut the diet in half on one day each week. The foods commonly employed in determining the tolerance for carbohydrate and protein are 5 per cent vegetables, oranges, oatmeal, potato, fish, chicken, lean meat.

1 gram protein	1 calorie	1 kilogram = 2.2 pounds.
" carbohydrate	4 " "	30 grams (g) or cubic centimeters
" fat	9 " "	(c.c.) = 1 ounce.
" alcohol	7 " "	A patient at rest requires 25 calories per kilogram body weight;
6.25 " protein contain 1g. nitrogen		approximately 1 calorie per kilo. per hour.

Consult Chemical Composition American Food Materials, Bull. 28, U. S. Dept. Agriculture, by sending 10 cents in coin to Supt. of Documents, Washington, D. C., also Annual Report Conn. Agricultural Experiment Station, New Haven, Conn., Food Products and Drugs, 1913, Part I, Section 1.—Free.

Water, clear broths, coffee, tea, cocoa shells and cracked cocoa can be taken without allowance for food content.

FOODS ARRANGED APPROXIMATELY ACCORDING TO CONTENT OF CARBOHYDRATES

	5%	10%	15%	20%	
VEGETABLES (fresh or canned)	Lettuce	Tomatoes	Pumpkin	Green Peas	Potatoes
	Cucumbers	Brussels	Turnip	Artichokes	Shell Beans
	Spinach	Sprouts	Kohi-Rahi	Parsnips	Baked Beans
	Asparagus	Water Cress	Squash	Canned	Green Corn
	Rhubarb	Sea Kale	Beets	Lima Beans	Boiled Rice
	Endive	Okra	Carrots		Boiled
	Marrow	Cauliflower	Onions		Macaroni
	Soybean	Egg Plant	Mushrooms		
	Sauerkraut	Cabbage			
	Beet Greens	Radishes			
	Dandelion	Leeks			
	Lentils	String Beans			
	Swiss Chard	Broccoli			
	Celery				
FRUITS	Ripe Olives (20% fat)	Oranges	Apples	Plums	
	Grape Fruit	Cranberries	Pears	Bananas	
	Lemons	Strawberries	Apricots	Pineapples	
		Blackberries	Blueberries		
		Gooseberries	Cherries		
Meat, Nuts		Peaches	Currants		
		Pineapple	Raspberries		
		Watermelon	Huckleberries		
	Butterfats	Brazil Nuts	Almonds	Peanuts	
	Pignolias	Walnuts	Walts (Eng.)		
	Unsweetened and Unsipped	Hickory	Bechnuts	10%	
	Pickles, Clams, Oysters, Peas	Peanuts	Pistachios		
	Scallops, Liver, Fish Roe, Fillets	Filberts	Pine Nuts	Chestnuts	

\* Reckon carb. in veg. of 5% group as 2% of 10% group as 6%.

	20 grams 10% 1. CARBOHYDRATES	PROTEIN	FAT	CALORIES
Oatmeal, dry wgt.	20	5	2	120
Cream, 40% .....	1	1	12	120
Milk .....	1	1	6	60
Brazil Nuts .....	2	5	20	200
Oysters, six .....	4	6	1	50
Meat (uncooked, lean) .....	0	16	2	50
" (cooked, lean) .....	0	8	2	55
Bacon .....	0	5	15	155
Cheese .....	0	8	11	135
Egg (whole) .....	0	6	6	75
Vegetables 2% group .....	1	0.5	0	10
Vegetables 10% group .....	0	0.5	0	6
Potato .....	6	1	0	30
Bread .....	18	3	0	90
Butter .....	0	0	25	225
Oil .....	0	0	30	270
Fish, cod, haddock (cooked) .....	0	6	0	25
Broth .....	0	0.7	0	3
Small orange or 1/2 grape fruit .....	10	0	0	40

Form J. S. Thomas & Co., Inc., 105 State St., Boston

Throughout the course of treatment the education of the patient in the hygiene of his life, in his diet and in the examination of his urine should be promoted. Like others, I have devised various forms of printed matter, and in fact have just completed for patients a sort of diabetic primer\* which I hope they will actually study. This is designed not only to educate the patient, but to save the physician's time.

Acidosis should be prevented by the rules of diet prescribed by the doctor and adopted by the patient. In general, given a patient without acidosis, one can avoid its onset. The elimination of fat at the beginning of treatment and its elimination later whenever signs of acid poisoning appear is a safe rule. I have not used alkalis for some years. Until a group of cases, more severe than the 15 already cited, is reported to have recovered by some other method, I recommend to your consideration the plan of treatment which has yielded these results.

### THE TREATMENT OF THREATENING DIABETIC COMA

The following rules are in force at the New England Deaconess and Corey Hill Hospitals:

1. **Nursing.**—Provide a special nurse for the patient both day and night, and, preferably, one trained in diabetic work.
2. **Bed.**—Keep the patient in bed and warm. Avoid loss of calories through exertion or exposure; if restless, protect from becoming chilled by flannel night-clothes. Every effort should be made to allay nervousness and discomfort.
3. **Bowels.**—Move the bowels by one or more enemata. Cathartics should usually be avoided for fear of causing diarrhea.
4. **Stomach.**—The stomach should be free from indigestible food. With adults, when in doubt, but with children in all cases, begin treatment with gastric lavage.
5. **Heart.**—Sustain the circulation with the help of digitalis. Caffein may be given subcutaneously, or as black coffee by rectum.

6. **Administration of Liquids.**—Give 1000 c. c. of liquids within each six hours. The liquids are to be given slowly, hot, as coffee, tea, thin broths, water; if the prospect is dubious of giving so much liquid by mouth, salt solution or tap-water is to be given by rectum; if this resource fails, the nurse should call the doctor to give intravenously the balance of the liter which remains not given for the period. (It will seldom be found necessary to give more than 1000 c. c. liquids, thanks to the avoidance of alkalis.) In order to secure the introduction of sufficient liquid in the first six hours the cleansing enema at the beginning of treatment should be followed after half an hour by an enema of 500 c. c. salt solution in all cases as a matter of precaution.

7. **Diet.**—If the patient has been accustomed to the fasting method of treatment, begin or continue the fast, but if he has been upon a full diet, give 1 gram of carbohydrate per kilogram body weight during the 24 hours in the form of orange

\* A Manual of Diabetic Treatment for Doctor and Patient. Lea & Febiger. Philadelphia, 1918.

juice or gruel (oatmeal) made with water; or as many grams of carbohydrate as the patient has voided in the urine in each successive preceding six hours. Whichever course is adopted, it is to be followed until danger is over.

8. *Alkalis*.—Avoid alkalis. If such have been previously given, omit at the rate of 30 grams a day.

Many diabetic problems demand solution to-day, and it is encouraging that they stand out in relief far more distinctly than ever before. Many of these problems do not require great discoveries for their elucidation, but simply plain hard work. Thanks to Dr. Allen, it is fortunate that so many of these can be worked out upon animals. By this means results can be more quickly secured.

1. The one question which I hope most to see solved within the next two years, is whether the tolerance of a mild diabetic for carbohydrate is lowered by our present methods of treatment in making him sugar-free. Perhaps Dr. Allen has already settled this point. Clinically, every once in a while one sees a patient with a high tolerance who loses the tolerance in a comparatively short course of time, although the best modern methods are followed. Thus Case No. 914, with a tolerance for 140 grams carbohydrate a year and a half ago, has now a tolerance for but 10 grams. This is so different from what I expected to occur in this case that I can hardly believe it necessary, and wonder whether some error in treatment has not been made. Of course it is possible that a year and a half ago by our former methods the tolerance would not have appeared nearly as high, and that at the start the case was really far more severe than was considered. I am sure that many of you have had similar experiences. We should not allow these apparently mild cases to change to severe without the sharpest possible fight. This question is of the utmost importance. Take, for example, two children in one family living not far from this city, who have apparently very, very mild diabetes. Should they be kept absolutely sugar-free or upon a restricted diet, but not a diet of undernutrition? This is the sort of a problem for the solution of which your wealthy diabetic should give your hospital \$50,000. It demands both clinical and experimental work, and it is justifiable to hold out the hope of securing useful results.

2. The next problem to interest me is whether the tolerance of the diabetic can be raised. Already considerable data have been accumulated at the Nutrition Laboratory of the Carnegie Institution by Benedict and myself, and eventually this will be published. In it are hints of such a possibility. The spectacular absence of sugar in the urine following the administration to the severe fasting diabetic of large quantities of levulose and of some other carbohydrates is encouraging. How these patients can bear so much carbohydrate at one time when at another a few leaves of lettuce cause glycosuria is hard to understand. The fact that repeatedly the respiratory quotient rises in such individuals is of significance, just as is the high respiratory quotient of severe diabetics during fasting.

3. The increased lipid content of the blood and the measures necessary to reduce it is a third problem. The 400 analyses of blood lipoids made by Gray upon my patients have interested

me greatly, and have shown the need for more. From them I am beginning to learn a few suggestions as to how the fat can be reduced. But when I heard the other day that in addition to the numerous analyses made under Dr. Allen's direction upon the blood lipoids of his patients there still remained 5000 more specimens to analyze, I could not help feeling that perhaps we were nearer to the discovery of the method by which the high blood fat could be reduced than we supposed.

4. The high blood sugar and its reduction in diabetes is a tempting target. Is this really worth while? I think it is, but I would be glad to have more evidence. When I see a patient who has outlived the average period of life of my living cases for the corresponding decade of age, who appears in good condition, as does Case No. 600, and yet shows a blood sugar of 0.21 per cent, but is sugar-free, I hesitate to change the method of treatment which has worked so well so many years. Time perhaps will settle this question for us, for who knows how long this patient has had so high a blood sugar? During the first five or six years of her treatment, no blood sugar test was made. To me it appears that she will live for many years to come, and although she may not reach her expectancy of life, which would mean a duration of the diabetes of 21 years in her special case, yet there appears to be a fair chance of her doing so. Would this patient really be benefited, now that she is sugar and acid free, by having her blood sugar brought to normal? I never see her without thinking, "Fools step in where angels fear to tread," and at present I want to be numbered with the angels.

5. Edema and even anasarca in the severe diabetic are symptoms often accompanied by well being on the patient's part. Why do some diabetics feel so much better when they have dropsy than when the water content in their tissues is normal or even below normal? At present I can remember but one of my diabetic patients who has shown marked dropsy who has not been freed of it by simple restriction of salt. Just recently I have reported<sup>6</sup> one case, Case No. 1012, where a gain of 25 per cent weight in the form of edema was present, and another patient now under my care has lost an equal amount. If patients do not go into coma when they have dropsy, why not make them have dropsy when coma is threatening? Dr. Hornor and I have partially attempted this in one case, but I would like to have it literally carried out and see the patient's weight increase not one or two pounds in the course of a day, but by 10 to 20 per cent. It would not do to inject so much fluid directly into the circulation because of the failing heart, but the fluid could be introduced under the skin or into the abdominal cavity.

These are only a few of the diabetic problems which you have to solve. Most of them appear capable of solution. They will not be settled except by aid from many workers, and in their solution not alone should the help of doctors and medical students be utilized, but that of technicians to the widest possible degree. While absorbed in our endeavors let us not forget that when a diabetic life is prolonged for even a day, fresh hopes for millions of diabetics throughout the world are created.

<sup>6</sup> Med. Clin. of North America, January, 1918.



## A STUDY OF AN AUTOAGGLUTININ OCCURRING IN A HUMAN SERUM

By MILDRED C. CLOUGH, M. D., and INA M. RICHTER, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

Autoagglutination, that is, agglutination of red blood corpuscles in the presence of serum from the same individual, is an extremely uncommon occurrence in human beings. Indeed, some authors (1, 2, 3) state that this never occurs. The following instance is reported on account of certain interesting observations brought out in a study of the autoagglutinin, as well as on account of the rarity of the condition. This phenomenon was first noticed in our case on making a routine red blood cell count. It was found upon drawing the blood into the diluting pipette that the red blood cells became agglutinated so markedly that clumps were visible macroscopically as well as microscopically. The agglutinated cells could not be broken up upon shaking, and an accurate count of them was impossible.

The literature on the subject of autoagglutination is very meager. The first reference to this phenomenon is by Reitmann (4) in 1890. He noted, on making a red blood cell count in a case of cirrhosis of the liver, that "the red blood corpuscles were strikingly sticky, three or four sticking together." No further observations on the blood are recorded, but it seems likely that this occurrence was due to autoagglutination. Ascoli (5) in 1901, stated that, in a study of the blood of 17 normal individuals, he found in a number of instances that the serum was able to agglutinate the red blood corpuscles of the same individual, as well as those of other individuals. This report, however, is open to question. It seems very improbable that this rare phenomenon should occur a number of times among only 17 specimens of blood examined. This surprising statement is probably to be explained by the fact that he apparently regarded rouleaux formation as a form of agglutination. Klein (6) in 1902, noticed autoagglutination in the blood of a horse and stated in this report that in 1890, in a case of hypertrophic liver cirrhosis, he was unable to make a red blood cell count, because the cells, when drawn into the diluting fluid, stuck together in masses in which the cell boundaries could scarcely be made out. He considered it a phenomenon peculiar to liver cirrhosis, and said that Obermayer in Nothnagel's clinic stated in a personal communication that he had confirmed Klein's observation in a series of cases of hypertrophic liver cirrhosis. Landsteiner (7) in 1903, again noted autoagglutination in the blood of horses and other animals. He found that the agglutinin was fixed to the cells at low temperatures, and if the washed, agglutinated red blood corpuscles were suspended in warm salt solution the clumps broke up, and agglutinin could be demonstrated in the salt solution. He considered that cold exerts a favoring influence on isoagglutination also, and that isoagglutinins can be partially liberated by warming (8). He isolated the auto- as well as the heteroagglutinins in the globulin fraction of the serum (9).

Hektoen (9) in 1906, stated that he observed autoagglutination and autophagocytosis in the blood of two individuals, but in a later article (10) said that "autoagglutinins are very seldom, if ever, demonstrable *in vitro*." Rous (11) has produced autoagglutination in the blood of rabbits, and Ottenberg and Thalhimer (12) report its occurrence in cat's blood.

The following is a brief abstract of the history of the patient in whose blood autoagglutination was observed:

CASE HISTORY.—Med. No. 38768. L. T.; 32 years; female. Russian Jew. Married. Adm. Oct. 19, 1917. Discharged Nov. 28, 1917. Family and past history negative. One week before admission the patient "caught cold," with fever, cough, dyspnea, palpitation, and pain in the right side of the chest. Physical examination on admission showed signs of a diffuse bronchopneumonia, and of mitral stenosis and insufficiency with auricular fibrillation. These findings were confirmed by X-ray and electrocardiographic examinations. Sputum culture showed both *B. influenzae* and *Staphylococcus aureus*. Blood culture and Wassermann reaction were negative. Urine normal, except for a trace of albumin, and, for a few days after admission, a trace of urobilin. The pulse ranged from 65 to 110; blood pressure from 100/50 to 120/70. The temperature ranged from 100°-104°, gradually falling to normal four weeks after admission. The blood findings on admission were: red blood cells, 4,736,000; white blood cells, 9600; hemoglobin 100 per cent. During the fever there was a polymorphonuclear leucocytosis of from 10,000 to 24,000. The hemoglobin fell to 70 per cent and the red cells to 4,000,000 at the height of the infection, but rose to 90 per cent and 4,900,000 on discharge. Except for the count made on admission, it was impossible to make a red blood cell count during the febrile period on account of the autoagglutination, unless the solution were warmed. With recovery and return to normal temperature, warming above ordinary room temperature was no longer necessary. The agglutinating activity of the serum then seemed to be somewhat feeble, and to require a lower temperature for its manifestation. We do not, however, attach very great significance to this observation for reasons which will be discussed later.

The phenomenon of autoagglutination was first noticed in our case on diluting the blood for a red cell count. New pipettes and new diluting fluids were used for a second count to eliminate the possibility that the agglutination was caused by dirty apparatus or improperly prepared solutions, but agglutination again occurred. It seemed obvious, then, that the peculiarity was inherent in the blood itself.

In order to study this phenomenon, it was necessary to obtain serum, and unagglutinated red blood corpuscles free from serum. It occurred to us that agglutination might be prevented if the blood were kept warm, and the red cells washed several times in warm salt solution. It seemed inconceivable that the red blood cells were agglutinated in the circulating blood, and this suggested that the phenomenon might have been initiated at least by a lowering of the temperature of the blood. Also, by analogy with the hemolysin of paroxysmal

hemoglobinuria, which is fixed only at low temperatures, it seemed possible that fixation of the agglutinin might be avoided by washing the blood at body temperature. The observations of Landsteiner (7, 8) on the favoring effect of cold upon iso- and autoagglutination also suggested this method of obtaining unagglutinated red blood cells free from serum.

Accordingly, 10 c. c. of blood were obtained by venapuncture with a warm syringe. Five cubic centimeters of blood were allowed to clot in a test-tube to obtain serum, and the remaining 5 c. c. were added to 100 c. c. of sodium citrate solution warmed to 37° C. This mixture was immediately centrifugalized, and the cells washed twice in warm salt solution, great care being taken to keep the temperature constantly at or near 37° C. No agglutination of the red blood cells occurred during the washing.

A small amount of the original blood citrate mixture was kept separate, and allowed to stand at room temperature. In a few minutes marked agglutination became apparent macroscopically and microscopically. After placing the mixture in the thermostat at 37° for a short time, the agglutinated clumps of red blood cells broke up. In a hanging drop preparation the individual cells were seen to be perfectly preserved and evenly distributed throughout the suspension. This mixture was now placed in the ice-chest for a few minutes, and agglutination reappeared, and again disappeared entirely after warming to body temperature. This procedure was repeated several times with the same result.

A one per cent suspension of the washed red blood cells was then made in salt solution. Chilling this suspension caused no agglutination. The addition of a little of the patient's serum to part of the suspension, however, caused marked agglutination of the patient's red blood cells when the preparation was chilled. This agglutination, likewise, disappeared on warming to 37° C.

From these experiments it seemed probable that the peculiarity of this blood was present in the serum and not in the red blood cells. In order to study the action of this serum on red blood cells from other individuals, and of other sera on the red cells of this individual, the group of the patient was determined by the method suggested by Moss (13). Microscopic preparations were made of the patient's serum with red blood cells from individuals of groups 2 and 3, and also of the patient's red cells with serum of groups 2 and 3. The following results were obtained:

1. Group 2 serum + patient's red blood cells. Room temperature. One hour. Agglutination. This was not increased by chilling the mixture, nor were the clumps broken up by incubation at 37° C.

2. Group 3 serum + patient's red blood cells. Room temperature. One hour. No agglutination either at room temperature or in the ice chest.

3. Patient's serum + group 2 red blood cells. Room temperature. One hour. Agglutination similar to that in preparation 1.

4. Patient's serum + group 3 red blood cells. Room temperature. One hour. Slight agglutination at room tempera-

ture, which became marked on chilling in the ice-chest, and which completely disappeared on warming to 37°.

One could conclude, therefore, from these tests that the patient belonged to group 3. The agglutination occurring in preparation 4 differed from ordinary isoagglutination in its disappearance at 37°, and was evidently identical with that caused by the action of the patient's serum on her own red cells. In order to test this further, another preparation was set up with group 4 red blood cells.

5. Patient's serum + group 4 red blood cells. Room temperature. One hour. Agglutination similar to that in test 4, disappearing completely on warming.

It follows from these tests that there is no peculiarity in the patient's red blood cells to account for the autoagglutination. The patient's red blood cells were not agglutinated by the serum of another individual belonging to group 3, while the red blood cells of other individuals of groups 3 and 4 were also agglutinated in this peculiar way by the patient's serum.

This serum, then, has two distinct types of agglutinating activity on human red blood cells, (1) the usual isoagglutinating activity manifested by sera from all individuals belonging to group 3 for cells from individuals of groups 1 and 2, (2) an agglutinating activity, manifested only at low temperatures for cells of the patient herself, and for cells of all individuals tested regardless of the blood group to which they belonged.

The substance causing the second type of agglutination must, therefore, be regarded as both an autoagglutinin and an isoagglutinin. Furthermore, as will be shown later, this substance has the power of agglutinating the red blood cells of various species of animals, and must, therefore, be a heteroagglutinin as well. However, we shall follow the custom of using the term autoagglutination for this phenomenon to distinguish it from ordinary isoagglutination and heteroagglutination, bearing in mind, however, that it does not fully define the agglutinating activity of the serum. A more accurate term would perhaps be "cold agglutination."

Fig. 1 shows the autoagglutination of the patient's cells by her own serum at room temperature. Fig. 2 shows the same preparation after warming. The clumps are nearly, but not entirely, broken up. Further warming would have resulted in complete separation of the cells. In preparations showing marked agglutination, the macroscopic and microscopic appearances are identical with those of cells agglutinated by an ordinary agglutinating serum. When the reaction is less marked, as in high dilutions of serum, or at temperatures only slightly reduced, the clumps are looser and the individual cells less distorted. In preparations showing minimal degrees of agglutination, the cells are simply assembled in small clusters, without heaping up of the cells or deforming of their outlines. No rouleaux formation was observed in the preparations.

The properties of the patient's serum were then studied in the following ways:

Progressively increasing dilutions of the serum were made (from 1-2 up to 1-4000). To 0.25 c. c. of each dilution was added an equal volume of a 1 per cent suspension of the

patient's red blood cells and the mixtures placed in the ice-chest. At the end of 30 minutes agglutination was evident macroscopically in all dilutions of the serum up to and including 1-250, and after 24 hours also in 1-500. (These figures represent the final dilutions of the serum after the addition of the red blood cell suspension). This agglutinating substance, then, was present in the serum in high concentration.

In order to determine the highest temperature at which agglutination was initiated, a similar series of tubes was set up. These tubes were then cooled by immersion in a water bath, the temperature of which was gradually reduced. Agglutination was determined macroscopically. The results are shown in the following protocol:

30°	Half hour.	No agglutination.
27°	"	"
24°	"	"
22°	"	Agglutination in dilutions of serum up to 1-4.
19½°	"	" " " " " " " " " 1 8.
17°	"	" " " " " " " " " 1 30.
15°	"	" " " " " " " " " 1 30.
12°	"	" " " " " " " " " 1 250.
Ice chest over night.		" " " " " " " " " 1-500.

A similar experiment with dilutions of serum to which were added red blood cells of an individual belonging to group 4 gave identical results, indicating that the patient's cells were neither more nor less resistant to the agglutinating activity of her serum than were normal cells. Both sets when maintained at 22° for three hours showed agglutination in dilutions of serum up to 1-60. The critical temperature, therefore, appeared to be about 22° C.

The above set of tubes was then warmed gradually to see at what temperature the agglutination would disappear. The following results were obtained:

25°	Half hour.	Agglutination unchanged.
30°	"	"
34°	"	partially broken up.
34°	One hour.	completely broken up.

This experiment indicated that agglutination persisted at a temperature higher than that necessary for its initiation.

In order to determine the nature of this autoagglutinating substance in the serum, further tests were carried out.

1. Heating the serum in 1-5 dilution at 60° for 1/2 hour did not diminish its activity, while heating to 65° for 1/2 hour destroyed entirely its ability to cause agglutination of the patient's red blood cells.

2. Dialyzing the serum in collodion sacs against physiological salt solution for 24 hours did not impair its agglutinating ability.

3. Extraction of the serum with chloroform did not remove these agglutinins.

4. Precipitation of the globulins from the serum by ammonium sulphate resulted in disappearance of the agglutinin from the serum. First the "euglobulin" was precipitated by the addition of 36 volumes per cent of a saturated solution of ammonium sulphate. The precipitate was washed in 36 per cent saturated solution of ammonium sulphate, and dissolved in physiological salt solution. The ammonium sulphate was

then removed by dialysis. This euglobulin solution caused marked agglutination of the patient's washed red blood cells in the cold, like that produced by untreated serum. The "pseudoglobulin" was next precipitated from the serum by the addition of saturated ammonium sulphate solution to a concentration of 44 volumes per cent. The precipitate was then washed with 44 per cent saturated solution of ammonium sulphate, filtered, dissolved in physiological salt solution, and dialyzed. This pseudoglobulin solution caused no agglutination of the patient's red blood cells. The serum from which euglobulin and pseudoglobulin had been precipitated was dialyzed to remove the ammonium sulphate, and tested with the patient's red blood cells. No agglutination occurred. It was clear, then, that this autoagglutinin was associated with the "euglobulin" of the serum, as has been demonstrated in connection with iso- and other agglutinins.

Further work on the nature of the agglutinin was done in connection with absorption experiments, and will be discussed with them in a later paragraph.

The serum of the patient was tested for the presence of an autohemolysin analogous to that occurring in the serum of patients with paroxysmal hemoglobinuria. As shown by Donath and Landsteiner (14) and others, the serum from these patients contains an autohemolysin which combines with the red blood cells only at low temperatures, and hemolyzes them on subsequent raising of the temperature. If a suspension of red blood cells is added to such a serum, and the mixture is first chilled and then incubated at 37°, hemolysis takes place, whereas no hemolysis occurs if the preparation is incubated without previous chilling.

The following preparations were set up, tubes 2 and 3 being control tests:

1. Patient's serum 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 0° C. 1 hour, 37° C. 2 hours.
2. Salt solution 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 0° C. 1 hour, 37° C. 2 hours.
3. Patient's serum 0.25 c. c. + patient's corpuscles 0.25 c. c. (1% suspension) 37° 2 hours.

No hemolysis occurred in the test or in any of the control preparations. Even after standing in the ice-chest over night there was no hemolysis, though autoagglutination was evident. It was thought, then, that an autohemolysin might still be present, but its action on the red blood cells might be prevented by a lack of the necessary amount of complement, as was the case in the hemoglobulinuric sera studied by Meyer and Emmerich (15). Accordingly, a similar series was set up with 0.1 c. c. of guinea-pig serum added to each tube. No hemolysis resulted. It seemed obvious, then, that the absence of hemolysis in the first experiment was not due to a lack of complement, and that probably no autohemolysin was present. In vivo experiments to demonstrate autohemolysis were not tried on account of the theoretical danger of causing intravascular agglutination.

Attempts were made to absorb out the autoagglutinin from the serum by digesting it with the homologous red blood cells, and interesting results were obtained. In the first experiment,



the digestion was carried out at 37° C. after an initial chilling, and in the second experiment at about 3° to 5° C.

1. Warm digestion. To 0.5 c. c. of the patient's serum were added 2.5 c. c. of a 10 per cent suspension of the patient's red blood cells. This mixture was kept at 3° C. for half an hour. Autoagglutination became very marked. The mixture was then warmed to 37° C. with resulting disappearance of the agglutination. The red cells were centrifugalized out, washed twice with warm salt solution, and suspended in salt solution. Chilling this suspension caused no agglutination, and hence the autoagglutinin had not been fixed, or remained fixed to the cells. The activity of the supernatant serum was tested by the addition of fresh red cells. Agglutination became marked on chilling this preparation. Therefore, the autoagglutinin was still present in the digested serum. The supernatant serum was again digested with the patient's red blood cells in the same way. These red cells were washed in warm salt solution, and the absence of any agglutinin fixed to the cells was demonstrated by their failure to become agglutinated on chilling them. The autoagglutinin was again demonstrable in the serum. One must conclude, therefore, that the autoagglutinin is not fixed to the cells, but remains free in the serum, when the digestion is carried out at body temperature.

2. Cold digestion. To 0.5 c. c. of the patient's serum were added 2.5 c. c. of a 10 per cent suspension of the patient's red blood cells. This mixture was kept at 3° C., and not allowed to become warm. Agglutination was marked throughout the experiment. The agglutinated red cells were centrifugalized out, and the supernatant serum tested for autoagglutinin. A preparation of this serum with fresh washed red blood cells showed no agglutination after prolonged chilling. Digestion with the homologous red cells in the cold had therefore absorbed the autoagglutinins completely from the serum. The sedimented red blood cells were washed twice with cold salt solution, and suspended in warm salt solution. The agglutination, which had been marked, disappeared in the warm solution, but reappeared on chilling this suspension again. The autoagglutinin, then, had not been removed from the cells by the cold washings. This suspension was warmed again, centrifugalized, and the supernatant fluid tested to see if the autoagglutinin had been liberated from the red cells on heating. This was found to be the case. The supernatant salt solution caused typical agglutination of fresh red blood cells in the cold. This solution did not cause agglutination of group 2 cells, nor of animal cells at 37°, and therefore did not contain normal isoagglutinin or heteroagglutinins. It contained the autoagglutinin isolated in purified form, and made possible a study of its activity undisturbed by other agglutinating substances in the serum. The sedimented red blood cells were washed twice with warm salt solution, and a suspension of them was chilled. No agglutination occurred, showing that the autoagglutinin had been entirely liberated from the red blood cells by warming.

By these experiments, therefore, it was shown that the autoagglutinin was not absorbed from the serum by digestion with red blood cells if the mixture were kept warm. If, how-

ever, digestion were carried out in the cold, the autoagglutinin was removed from the serum and fixed to the red blood cells. The physical or chemical process involved in the union was, however, a reversible one, and caused no permanent change in the red blood cells, since the autoagglutinin could be entirely liberated from the red blood cells by warming them, and since these red blood cells were now agglutinable by fresh serum.

These warm and cold absorption experiments were repeated, digesting the patient's serum with cells from an individual belonging to group 4. Exactly the same results were obtained. Removing the autoagglutinin from the patient's cells by cold digestion removed also that for group 4 cells, and vice versa.

The patient's serum from which the autoagglutinin had been absorbed was then tested to see if the ordinary normal isoagglutinin for group 2 cells had been removed also. This was found not to be the case. The absorbed serum caused marked agglutination of group 2 cells at 37° C., which was not increased by chilling. The isoagglutinin had not been affected by absorption of the autoagglutinin.

The isoagglutinin for group 2 cells was then absorbed from the patient's serum. Digestion of 0.5 c. c. of the serum with 0.1 c. c. of group 2 red blood cell "mush" at 37° for half an hour, absorbed completely the isoagglutinin. A preparation of this absorbed serum with fresh group 2 cells showed no agglutination when kept in the thermostat. However, when this preparation was placed in the ice-chest, a marked agglutination occurred, which disappeared on warming. This absorbed serum also agglutinated the patient's red blood cells, and cells from other individuals of groups 3 and 4, on chilling, with disappearance of the agglutination on warming. In this experiment, therefore, it was shown that the isoagglutinin for group 2 cells could be absorbed independently of the autoagglutinin, and that red blood cells of group 2, like those of groups 3 and 4, were susceptible to the action of the "cold" or "autoagglutinin."

It was also possible to demonstrate that the patient's serum possessed the property of causing "cold" agglutination of the red blood cells of other animals, in addition to ordinary heteroagglutination, and that the agglutination of these cells was brought about by the same substance which was active on human cells. This could be shown very easily with hen's cells, since no heteroagglutinins were present in the serum against the blood of the two hens used. Mixtures of this serum with washed hen's cells showed no agglutination at thermostat temperature, but marked agglutination at ice-box temperature. This agglutination broke up on warming the mixture, exactly as did the autoagglutination of human cells, and reformed on subsequent cooling.

Tests were also made with sheep, guinea-pig, rabbit, pig, and cat red blood cells. Heteroagglutinins were present in the serum for these species of cells. At first it was thought that these might be eliminated by using progressively increasing dilutions of serum for the tests, since the autoagglutinin, though much feeble than in the first experiments, was still present in fairly high concentration (about 1-100). The following tests were set up to determine the titer of the hetero-

agglutinins for these cells. After incubating at 37° for one hour, the degree of agglutination was noted, and the preparations were then chilled, and a second observation made. The following results were obtained:

Dilutions of patient's serum + sheep cells	Final serum dilution	37° hr.	Chilled	37°
1-10 .....	1-20	++++	++++	++++
1-20 .....	1-40	0	++++	0
1-40 .....	1-80	0	0	0
1-80 .....	1-160	0	0	0

Dilutions of patient's serum + guinea-pig cells	Final serum dilution	37° 1 hr.	Chilled	37°
1-10 .....	1-20	0	++++	0
1-20 .....	1-40	0	+++	0
1-40 .....	1-80	0	0	0
1-80 .....	1-160	0	0	0

Dilutions of patient's serum + rabbit cells	Final serum dilution	37° 1 hr.	Chilled	37°
1-10 .....	1-20	++++	++++	++++
1-20 .....	1-40	+++	++++	++++
1-40 .....	1-80	++	++++	+
1-80 .....	1-160	+	+++	+

In the test with sheep cells, a dilution of serum of 1-20 sufficed to eliminate heteroagglutination. The "autoagglutinating" activity of the serum on sheep cells could then be demonstrated by chilling this mixture. This was better shown with the guinea-pig cells. Serum diluted 1-10 caused no heteroagglutination of the guinea-pig cells, while "autoagglutination" occurred with serum diluted up to 1-40. The results with the rabbit red blood cells are less definite, since heteroagglutination was present even with the serum diluted 1-80.

More conclusive results were obtained by digesting the patient's serum at 37° C. with sheep, guinea-pig, cat, pig, and rabbit red blood cells to remove the heteroagglutinins for these cells.

The patient's serum was digested with sheep cells (0.5 c. c. serum + 0.3 c. c. sheep cell "mush") at 37° for one hour. The cells were then removed by centrifugalization, and fresh sheep cells added. No agglutination occurred at 37°, showing that the absorption of heteroagglutinin was complete. On cooling this mixture, agglutination became marked, and on warming again it broke up exactly as did the autoagglutination of the patient's cells.

Heteroagglutinins for guinea-pig, cat, and pig cells were removed in the same way, and the activity of the "autoagglutinin" on these cells could then be demonstrated.

Heteroagglutinin for rabbit cells was also removed from the serum by digesting 0.5 c. c. of serum with 0.2 c. c. rabbit cell "mush" at 37° C. A preparation of this absorbed serum with fresh rabbit cells showed no agglutination at body temperature, but marked agglutination at ice-box temperature, which could be broken up on warming. That is to say, the heteroagglutinin was absorbed, leaving the autoagglutinin, which was active on rabbit cells. The absorbed serum was shown to still possess the autoagglutinating activity on group 4 red blood cells. Mixtures of this serum with guinea-pig cells and with sheep cells showed agglutination at 37°, demonstrating that the hetero-

agglutinins for these cells had not been affected by removing the heteroagglutinin for rabbit cells. It was further shown that this absorbed serum also contained the isoagglutinin for group 2 cells.

We then tried to absorb the autoagglutinin from this serum from which the heteroagglutinin for rabbit cells had been removed, by digesting it with 0.3 c. c. rabbit cell mush at ice-box temperature. The agglutinated cells were then removed by centrifugalization in the cold, and fresh rabbit cells were added to test the completeness of the absorption. Agglutination occurred when the mixture was chilled, showing that the serum was not exhausted. Three further digestions, each with 0.2 c. c. of rabbit cell mush, were necessary before absorption of the autoagglutinin was complete. We then tested the agglutinating activity of the serum for human group 4 red blood cells. Cooling this mixture caused no agglutination. Therefore, removal of the "autoagglutinin" for rabbit cells had also removed the "autoagglutinin" for human cells. That this disappearance of agglutinin was the result of a specific agglutinin absorption and not merely a non-specific mechanical removal by the relatively large quantity of cells used in the digestion, is indicated by the fact that the exhausted serum still retained, practically undiminished, its heteroagglutinins for guinea-pig and sheep cells, and its isoagglutinin for group 2 human cells. It seems probable, therefore, that the same substance was responsible for the "autoagglutination" of both rabbit and human cells.

The action of the autoagglutinin on the cells from different species of animals was also studied by means of the "purified agglutinin" already described. The autoagglutinin was absorbed from the serum by digestion in the cold with group 4 human red blood cells, and after washing the cells in cold salt solution several times, the autoagglutinin was liberated in warm salt solution. A solution of purified agglutinin was also prepared by absorbing it from the serum in the same way with rabbit cells. These solutions containing purified agglutinin were tested with rabbit, sheep, and guinea-pig red blood cells, and with human red blood cells of groups 2 and 4. No agglutination occurred in any of the mixtures at 37°. Agglutination became evident, however, in all of the preparations upon chilling, and disappeared upon warming them. These purified autoagglutinin solutions, then, contained no hetero- or isoagglutinin, as far as tested, but only the autoagglutinin which was shown to be active on all the species of red blood cells tested. This purified autoagglutinin, isolated by digestion of the serum with human red blood cells, was identical in its behavior with that obtained by means of animal (rabbit) red blood cells. One must conclude, therefore, that the autoagglutinin is a single substance, which, unlike iso- and heteroagglutinins is not specific, but is active on the red blood cells of different species of animals.

The action of the autoagglutinin was next tested on cells other than blood cells. An emulsion of epithelial cells from the urinary tract was prepared by centrifugalizing normal urine. As would be expected, the patient's serum did not cause any agglutination of these cells at 0° or at 37° C.

We attempted to study the chemical nature of the autoagglutinin, and particularly to determine whether or not it could be freed from proteid. The results obtained so far are inconclusive on account of the small amount of serum available. We found that, like other agglutinins, it was precipitated from the serum with the "euglobulin" fraction of the proteid by the addition of 36 volumes per cent of a saturated solution of ammonium sulphate. The fact that the agglutinated red blood cells, after being washed free from serum with cold salt solution, give up the agglutinin on warming, suggested that this method might be used to obtain the active substance in a relatively pure form, free from the ordinary proteid constituents of the serum.

Landsteiner and Jagić (16) have used a similar method in the study of the heteroagglutinin for goose red blood cells in beef serum. They found that this agglutinin is best absorbed in the cold, and is partially liberated on heating to 50° C. They digested a large volume of beef serum with thoroughly washed goose cell stroma in the cold, washed the agglutinated stroma in the cold, then suspended it in salt solution, and liberated the agglutinin by heating. This solution contained 0.2 per cent proteid, as compared with 6.6 per cent in the original serum. The agglutinin was precipitated from this solution with ammonium sulphate. However, the solution still contained considerable proteid independent of agglutinin, since most of the agglutinin could be removed by the addition of fresh stroma, leaving behind in the solution most of the substances giving the tests for proteid. They did not attempt further purification by repeating the procedure.

In making the tests for proteid, we used Heller's nitric acid test, since it was found to be much more sensitive for the proteids of serum than were the ordinary color reactions. Preliminary tests showed that normal horse serum in 1-2000 dilution gave a positive reaction with Heller's test, whereas Millon's and the biuret reaction were positive only in concentrations of 1-125, or higher.

Fresh red blood cells were used at first in the test but were found to be unsatisfactory. They could easily be washed free from serum, but after agglutination the mechanical injury incurred during the washings, together with the repeated warming and chilling, caused slight hemolysis, with liberation of sufficient hemoglobin to give a positive Heller's test. No better results were obtained by using red blood cells fixed in 1/2 per cent formalin. These cells absorbed agglutinin from the serum exactly as did fresh red blood cells. The different manipulations, however, caused some hemolysis of these cells also.

More satisfactory results were obtained by using stroma prepared by laking red blood cells belonging to group 4 with distilled water, and washing this red blood cell stroma several times. These laked red blood cells absorbed agglutinin from the serum in the cold, became agglutinated, and gave up agglutinin when warmed, with disappearance of agglutination, exactly as did fresh red blood cells. To 0.25 c. c. of thoroughly washed stroma was added 0.5 c. c. of the patient's serum. This was chilled in ice water half an hour. Macroscopic floc-

culi became visible in the suspension. After centrifugalizing cold the supernatant serum was pipetted off, and the stroma suspended in warm salt solution, in order to break up the clumps and to permit thorough washing. After the clumps were broken up the mixture was again chilled and centrifugalized. The supernatant salt solution was tested for proteid by Heller's test. After this had been repeated three times, the supernatant salt solution no longer gave a positive Heller's test. The stroma was then suspended in salt solution, and warmed to liberate the autoagglutinin, and the salt solution was centrifugalized free from stroma. This solution was shown to contain autoagglutinin by testing it with fresh group 4 cells, though the activity of the solution was not as marked as that of the original serum, and had evidently been weakened by the repeated manipulations. Heller's test was negative with this agglutinin solution, and the addition of ammonium sulphate to it caused no visible precipitate. By this method, therefore, we were able to obtain an agglutinating solution which gave a negative Heller's test, and hence contained less proteid than is contained in a 1-2000 dilution of serum. Though these results are suggestive, we cannot conclude definitely that this agglutinin is not a proteid, since the limited quantity of serum available did not permit of further tests.

In order to differentiate this autoagglutination more clearly from rouleaux formation, a similar study was made of this phenomenon. This work is still incomplete, and a more detailed report of it will appear in a later paper. Certain differences in these two phenomena may be mentioned here. As pointed out by Decastello and Sturli (17), and by Sellards (3), and confirmed in our experiments, serum is able to cause rouleaux formation only in high concentrations. In the sera which we studied, a dilution of 1-4 was sufficient to destroy this activity. The autoagglutinating serum, on the other hand, was active after dilution to 1-500. These authors also point out that the property of the serum of stimulating rouleaux formation, and that of the red blood cells of becoming clumped in rouleaux is very unstable, and disappears within a few hours, or, at most, a few days. This was true in our experiments with rouleaux-forming serum, while the serum causing autoagglutination has remained active, with but slight diminution in strength, for several months. Fresh cells were not necessary for demonstrating autoagglutination. Heating the rouleaux-forming serum to 65° for 1/2 hour increased definitely its activity, as noted by Sellards (3), while heating the autoagglutinating serum to this point entirely destroyed its activity.

In our experiments, the formation of rouleaux seemed not to be affected by raising or lowering the temperature of the mixture, as was the agglutination of red blood cells by the autoagglutinating serum. After preparations showing rouleaux formation had stood at room temperature for several hours, the rouleaux broke up much as did the clumps of autoagglutinated red blood cells. This breaking up of rouleaux, however, occurred at low temperatures as well as at body temperature and, after it once occurred, no reformation of the rouleaux could be obtained. We found that the rouleaux stimulating substance could not be absorbed from the serum even by



repeated digestions with large quantities of red blood cells, whereas the autoagglutinin could readily be absorbed. Certain points of resemblance between these two active substances were brought out in our studies. Both were active on cells from other individuals. Both substances were precipitated from the serum with the "euglobulin" by the addition of 36 volumes per cent of saturated ammonium sulphate solution. Both substances remained in the serum after dialysis in a collodion sac. However, in the case of the rouleaux-forming serum, dialysis could only be carried out for 24 hours, because the activity of this serum disappeared on longer standing. From these observations it seems clear that autoagglutination and rouleaux formation are entirely different phenomena.

#### DISCUSSION

The question then came up, is the phenomenon of autoagglutination in this patient's blood in any way related to the disease for which she entered the hospital? To settle this point, we studied the blood again during convalescence, shortly before her discharge from the hospital. Red blood cell counts could then be made without using warm solutions. Red blood cells and serum were obtained as before. Progressive dilutions of serum were made as previously and red blood cells added. Agglutination occurred only in dilutions under 1-16, and only at temperatures below 11° C. To again test out this point, other specimens of serum and red blood cells were obtained two months after the patient had recovered from her pneumonia. This time care was taken to keep the blood warm while it was clotting, and until the serum was removed, to prevent any fixation of the autoagglutinin to the cells in the clot, with resulting reduction in the strength of the serum. Autoagglutination again occurred in dilutions up to 1-16, and at temperatures below 15° C. At this time a few drops of blood were obtained from a daughter of the patient, and a similar autoagglutinin was found in this blood. It appeared to be somewhat feebler than that present in the mother's serum, but the amount of blood obtained was insufficient for further tests. It is obvious, therefore, that this peculiarity was quite independent of the disease from which the patient was suffering, and was an individual peculiarity, apparently hereditary. The increased strength of the agglutinin during the early part of her disease may have been related in some way to the infection, or may have been purely accidental.

#### SUMMARY

Autoagglutination, or agglutination of red blood cells by serum from the same individual, was observed in the blood of a patient admitted to the hospital on account of a bronchopneumonia associated with chronic mitral endocarditis.

Agglutination occurred only at low temperatures (below 22° C.), and broke up if heated to body temperature. Agglutination could be reproduced by again chilling the same preparation.

This serum caused similar agglutination of red blood cells from other individuals of the same blood group (group 3), and

also of group 4. (It contained ordinary isoagglutinins active at body temperature for cells of members of groups 1 and 2.) The cells of the patient washed free from serum showed no tendency to agglutination, and behaved exactly as did cells from other individuals of group 3. Hence the phenomenon depended solely on a peculiarity of the serum, and not of the cells.

The active substance in the serum had many of the properties of an ordinary agglutinin. It was active in fairly high dilution (up to 1-500). It resisted heating to 60° C. for 1/2 hour, but was destroyed at 65° C. It remained active after preservation in the ice-box for several months. It was not dialyzable. It was not removed by extraction with chloroform. It was precipitated with the "euglobulin" by 36 volumes per cent of saturated ammonium sulphate solution. It was absorbed from the serum during the process of agglutination (at low temperatures).

It was entirely distinct from the ordinary isoagglutinins in the serum, since either one could be removed from the serum, leaving the other intact.

The autoagglutinin differed from ordinary agglutinins in the following ways: 1. It was active only at low temperature, the agglutination breaking up on warming. 2. It was absorbed from the serum only at low temperature, and was liberated from the cells on warming. 3. It was active on red blood cells from all of the different species of animals with which it was tested (man, rabbit, guinea-pig, hen, sheep, cat, and pig). That the same substance was concerned in the agglutination of human cells and of cells from these different animals, and that it was distinct from the ordinary heteroagglutinins, which were also present in the serum, was shown by the absorption tests already described.

An attempt was made to study the chemical nature of the autoagglutinin, especially its relation to proteid, but the results were inconclusive. By liberating the agglutinin from washed, agglutinated red blood cell stroma in warm salt solution, a solution of agglutinin was obtained which gave a negative Heller's test and showed no precipitate on the addition of ammonium sulphate. This solution, therefore, contained less proteid than is contained in a 1-2000 dilution of horse serum. Further tests were impossible on account of the small supply of serum available, and the weakening of the autoagglutinin caused by the manipulations.

No autohemolysis was present in the serum.

A similar study of rouleaux formation was made in order to differentiate it more clearly from autoagglutination. The substance causing rouleaux formation resembled the autoagglutinin in that it, also, was active on cells from other individuals. Both substances were precipitated from the serum with the "euglobulin," and neither was dialyzable. Unlike the autoagglutinin, the rouleaux-forming substance was active only in concentrated serum. Its activity rapidly disappeared upon standing, and fresh cells were necessary for the formation of rouleaux. Rouleaux formation occurred equally well at high or low temperatures. Heating the serum to 65° C. increased its rouleaux-forming power. This substance was not absorbed

from the serum by the cells in the process of rouleaux formation.

The presence of the autoagglutinin was probably not related in any way to the disease from which the patient was suffering. It persisted with slight variation in strength for a period of two months' observation, and was found to be present in the serum of a daughter of the patient. Hence it was probably not a pathological phenomenon, but an individual, hereditary peculiarity.

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## A SIMPLE METHOD FOR THE DETERMINATION OF VENOUS PRESSURE<sup>1</sup>

By N. WORTH BROWN, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

A convenient instrument for the measurement of pressure within peripheral veins may be easily constructed from an ordinary mercurial manometer. The apparatus consists of a single-limb manometer in which water, carbon tetrachloride (Carbena) (Sp. Gr. 1.5) or bromoform (Sp. Gr. 2.5) is substituted for mercury. To the manometer is connected a small, saddle-shaped cup, 2 cm. in diameter, covered with the thinnest rubber tissue obtainable. This membrane must be loosely applied and should permit free oscillation without tension. A rubber bulb with thumb-screw compressor regulates the pressure within the manometer. The use of carbena or bromoform instead of water is advocated because of higher specific gravity and lower viscosity. Carbena is preferred for routine observations. The readings are easily reduced to water pressure.

The principle employed is that described by von Basch in 1876 for the determination of arterial pressure.<sup>2</sup> Oliver<sup>3</sup> and Sewall<sup>4</sup> have published studies on venous pressure obtained in a somewhat similar manner but using a spring pressure gauge applied directly over the vein. The manometer devised and used by Hooker<sup>5</sup> and later by Clark<sup>6</sup> has been used for some time in this institution and the observations made with it have demonstrated the value of venous pressure estimations in the clinical study of cardio-vascular and pulmonary disease.

The method here described differs from that used in recording venous pressures with the Hooker manometer. With the



FIG. 1—Venous Pressure Apparatus.

latter, a glass cup is cemented to the skin and the pressure necessary to obliterate the vein is determined by direct inspection through the cup, of the collapsed vessel; in this, the pres-

<sup>1</sup> Presented before The Johns Hopkins Medical Society, May 21, 1917.

sure required to prevent the return flow is measured and the appearance of a venous "wave" marks the reading point. It is desirable to use a prominent superficial vein in which the valves are effective. Pressure in the manometer is raised several centimeters and the cup, or capsule, is placed upon the vein with sufficient pressure to obstruct the return flow. The vein on the proximal side of the capsule is emptied by stroking in the direction of venous flow. The pressure in the manometer is allowed to fall by opening the needle valve. When the venous pressure equals the manometer pressure the vein above the capsule will rapidly fill. A reading at this time will give the approximate venous pressure.



FIG. 2.—(a) Before pressure is applied. Pressure in the vein is greater than within the capsule.

(b) Capsule pressed downward. Lumen of the vein obliterated. Pressure in the capsule is greater than in the vein.

(c) Capsule is slowly raised. When the pressure in the vein equals that within the capsule, blood will pass through the partly compressed vessel. The manometer reading at this point indicates the venous pressure.

After this preliminary observation the capsule is inflated but not distended (0.5 cm. water pressure) and the manometer valves are closed. The capsule and manometer now form a closed circuit. Repeated readings can be made by pressing down the capsule, stripping the vein and slowly raising the capsule, observing the height of the column in the manometer when the venous flow first returns. If reasonable care is exercised, the variations should not exceed one centimeter. Mechanical factors, which may under certain conditions influence results thus obtained, are constant and so insignificant that for clinical purposes they may be disregarded. It is important that the capsule be so adjusted that its margin does not compress the vein. As with all methods of estimating venous pressure the vein employed must be at the heart level.

For the fluid manometer may be substituted an aneroid adjusted to record low pressures in centimeters of water.

Simultaneous observations made with Hooker's venous manometer and with this apparatus give approximately the same results. Normal pressures, so far observed, when taken upon individuals resting quietly in the recumbent position with the arm extended and the hand at the heart level give readings between 3 and 9 cm.  $H_2O$ . Two cases of essential hypertension had pressures within normal limits. A well compensated aortic stenosis showed an average of 8.1 cm. Two patients with valvular lesions and auricular fibrillation had venous pressures ranging from 12 to 18 cm. of water. An uncompensated aortic regurgitation during the periods of dyspnea showed a pressure of 26 cm. A patient with obstruction in the superior vena cava gave a peripheral pressure of 14.6 cm., while the thoracic, at the same level, serving as a collateral, showed a pressure of 12.7 cm. Thrombosis of the left subclavian vein produced a pressure of 30 cm. in the left hand, whereas on the unaffected side it measured only 16 cm.

From these limited observations we are led to believe that readings with this instrument of 10 cm., or lower, represent normal venous pressures. In cardiac lesions pressures between 12 and 18 cm. suggest moderate decompensation, whereas constant pressures of from 20 to 30 cm., or over, indicate venous stasis and serious myocardial insufficiency.

The advantages of the method described are obvious. The determinations are equal in accuracy to any method except that which depends upon the introduction of a canula. The simplicity of the apparatus, its ease of manipulation, the rapidity with which observations can be made and an unmistakable reading-point, will commend its use for clinical purposes.

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## ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin.  
Prepared by the Authors.

### THE MAINTENANCE DIET IN DIABETES MELLITUS AS DETERMINED BY THE NITROGEN EQUILIBRIUM

By HERMAN O. MOSENTHAL and SAMUEL W. CLAUSEN

(From the Medical Clinic of The Johns Hopkins Hospital)

In the treatment of diabetes mellitus, there are two guiding principles which determine the caloric value of the diet. In the first place, the quantity of carbohydrates, proteins and fats offered the patient must be within his carbohydrate tolerance; that is, the diet must be so regulated that the urine remains

sugar free. It is generally acknowledged that under these circumstances the disease itself is treated in the most effective manner. Secondly, a diet of sufficient caloric value should be offered the patient, so that his health and strength may be maintained at a normal level. It is readily appreciated that these two guiding principles of treatment are diametrically opposed to one another in many respects. The one demands a restricted diet, and in many instances, undernutrition; the other calls for a larger amount of food. The first aims at treat-



ing the disease, diabetes mellitus; the second attempts to conserve the nutrition of the patient. The neglect of either factor may entail undesirable results.

During the past years, emphasis has been continually placed upon the dietary restriction and the prevention of glycosuria. Previously, on account of lack of full appreciation of the results which could be obtained by a more drastic curtailment of the food calories, this idea was not pushed to its logical conclusion of controlling the glycosuria of nearly every diabetic patient. Through the efforts of F. M. Allen, by systematic and radical reduction in the food, this may be easily accomplished in most cases.<sup>1</sup> The widespread use of these very limited diets has brought up the question of how little the individual may eat and yet remain physically and mentally fit. It is the object of the present paper to furnish at least a partial answer to this problem.

The standard for maintenance for the diabetic may be sought in one of two criteria; first, the caloric requirement, and second, the nitrogen equilibrium. The caloric requirement may be readily ascertained according to the height-weight formula of Du Bois and Du Bois.<sup>2</sup> Food administered in accordance with this standard<sup>3</sup> should satisfy all theoretic demands. The nitrogen equilibrium represents the lowest possible diet which could be exacted of any patient. Food, under these circumstances, results in the conservation of the protein tissues, but does not necessarily prevent the loss of fat. This principle has been applied in the treatment of obesity; it was successfully used in the prolonged dietetic experiments of Chittenden on normal people, and is employed here. No living being can afford to lose muscle and glandular tissue indefinitely. How far the fat store of any individual may be depleted with advantage is another question. There is much to be said in favor of allowing the diabetic to become thin, so that his metabolism may be established at a lower level, as has so frequently been urged, but it should be distinctly appreciated that this loss of weight should occur in the fats and not in the vitally necessary proteins. It is with these ideas in mind that the nitrogen equilibrium has been chosen as the lowest possible food standard by which diabetics may be maintained in a state of physical and mental well-being over longer periods.

Table 1 presents a summary of some of the cases studied. All of these patients were given diets of the same relative proportion of fats and proteins. These two food substances were maintained equal to each other, gram for gram, as nearly as possible. Only such carbohydrates were given as were unavoidably present in the green vegetables. In this way, these patients received diets which made a comparison as to the effect on the nitrogen equilibrium possible. From the table it may be noted that diabetic patients may be established in nitrogen equilibrium by a carbohydrate-free diet having a caloric value

equal to the standard total caloric requirement. In many instances, this may be accomplished at a considerably lower level of feeding. The lowest diet which will conserve the physical and mental efficiency of the diabetic is that which maintains the nitrogen equilibrium. A rough estimate for clinical purposes of what constitutes a maintenance ration for

TABLE 1

CALORIC REQUIREMENT NECESSARY TO PRODUCE NITROGEN EQUILIBRIUM IN CASES OF DIABETES MELLITUS, AS COMPARED WITH THE NORMAL METABOLISM OF INDIVIDUALS OF THE SAME AGE AND SEX. A SUMMARY OF SOME OF THE CASES STUDIED

Case	Age	Sex	General condition	Calories per hour per square meter of body surface			Caloric requirements necessary to establish N equilibrium as compared with normal metabolism
				Highest at which N equilibrium was not obtained	Lowest at which N equilibrium was obtained	Normal metabolic	
1. Period 1.	38 M.		Very poor	41.6	47.2	43.7	8 per cent higher
Period 2.				41.6	47.4	43.7	8 per cent higher
2. ....	35 F.		Fair	31.6	39.7	40.6	Unchanged
3. ....	43 M.		Poor	36.3	43.7	43.7	Unchanged
4. ....	56 F.		Normal	18.2	27.0	36.0	25 per cent lower
5. ....	26 M.		Fair	...	35.9	43.7	18 per cent lower
6. ....	35 M.		Normal	33.8	28.2	43.7	28 per cent lower
7. ....	41 M.		Normal	45.6	49.1	43.7	12 per cent higher
8. Period 1.	13 M.		Normal	49.7	39.5	54.9	28 per cent lower
Period 2.				37.7	51.7	54.9	6 per cent lower
9. ....	12 F.		Poor	36.4	...	...	...

\* Basal metabolism according to F. C. Gephart and E. F. Du Bois (Arch. Int. Med. 1916, XVII, 902), plus 10 per cent (to allow for the specific dynamic action of the diet.

the diabetic on a carbohydrate-free diet is from 1500 to 2000 calories. In adjusting the value of the diet, it should be borne in mind that women and small individuals generally require less food than men and larger individuals.

Certain other facts were developed in the course of this study which are not brought out in the table, but which may be briefly summarized as follows: The factors which determine the dietary level at which a diabetic maintains a nitrogen balance are apparently very numerous and not fully determined; glycosuria at times, and infections, even of very slight degree, may necessitate a higher diet to bring about the desired result. A marked assimilation of nitrogen may occur in diabetics while on a carbohydrate-free diet.

#### THE EFFECT OF DIET ON BLOOD SUGAR IN DIABETES MELLITUS. (Abstract)

By HERMAN O. MOSENTHAL, SAMUEL W. CLAUSEN and ALMA HILLER  
(From the Medical Clinic of The Johns Hopkins Hospital)

Aside from its physiological interest, it was hoped that this investigation would yield information which would enable the clinician to interpret blood-sugar values taken at any time of the day. The blood sugar was determined at hourly intervals in cases of diabetes mellitus. The patients were ordered diets which were adjusted to the therapeutic needs of the individual.

<sup>1</sup> Allen, F. M.: Boston Med. and Surg. Jour., 1915, CLXXII, 241.

<sup>2</sup> Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1916, XVII, 863.

<sup>3</sup> Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, XVII, 902.

that is, they were "carbohydrate-free," containing no starch except that present in green vegetables, or, except in a very few instances, limited in starch content so that the glycosuria was held in abeyance or at a low level. The results obtained under these circumstances, while they do not exhaust the subject from the physiological or pathological physiological point of view, are applicable to the practical interpretation of blood sugars in the treatment of diabetes mellitus.

TABLE 1

SUMMARY OF THE HOURLY DETERMINATIONS OF BLOOD SUGAR IN CASES OF DIABETES MELLITUS ON A CARBOHYDRATE-FREE DIET, OR ONE CONTAINING A MODERATE AMOUNT OF STARCH. IF THERE IS A RISE OF BLOOD SUGAR IN THE COURSE OF THE DAY, THE MAXIMAL VALUE REACHED ONE OR TWO HOURS AFTER BREAKFAST IS USUALLY NOT EXCEEDED TO ANY MARKED DEGREE AFTER LUNCH OR SUPPER. THERE FREQUENTLY IS A DIMINUTION IN THE GLYCEMIA IN THE AFTERNOON AND EVENING.

Fasting	Blood sugar per cent					
	After breakfast		After lunch		After supper	
	Maximal	Minimal	Maximal	Minimal	Maximal	Minimal
.18	.18	.17	.17	.13	.17	.11
.45	.45	.45	.45	.45	.45	.45
.23	.23	.23	.23	.23	.23	.19
.33	.33	.33	.33	.32		.28
.18	.18	.18	.19	.18	.18	.18
.17	.17	.17	.18	.18	.18	.18
.12	.19	.16	.20	.16	.16	.14
.15	.19	.15	.19	.11	.17	.15
.14	.16	.16	.18	.16	.16	.16
.13	.16	.13	.14	.08	.18	.15
.16	.25	.23	.23	.22	.26	.22
.14	.17	.14	.17	.17	.17	.15

The maximal percentage of blood sugar occurring in diabetic individuals on a carbohydrate-free diet, or one containing a moderate amount of starch, may be obtained one to two hours after breakfast. The glycemia may rise somewhat higher after lunch or supper, but never to any marked degree. On the other hand, the blood sugar may fall considerably in the afternoon and evening hours, leading to erroneous interpretations if taken only at this time of the day (Table 1).

In diabetic cases there is a tendency for the blood sugar to remain constant throughout the day while on a protein-fat diet, if the fasting blood sugar is high; on the other hand, if the fasting blood sugar is low, that is, if it has been reduced by previous dietetic treatment, there is an increase in the glycemia after carbohydrate-free food, which may become very marked (Table 1). This leads to the conclusion that diabetic patients, by raising their fasting or basal blood sugar percentage, tend to adjust their carbohydrate metabolism in such a manner that they are able to utilize the food offered them to better advantage. It may be desirable, therefore, not to attempt to reduce the blood sugar to a normal value in all cases of diabetes mellitus.

# A RARE TYPE OF BLADDER ULCER: FURTHER NOTES. WITH A REPORT OF EIGHTEEN CASES<sup>1</sup>

By GUY L. HUNTER, M. D., Baltimore, Md.

(Abstract from the Journal of the American Medical Association, 1918, Vol. LXX, 203.)

The author refers to his original publication in The Transactions of the Southern Surgical and Gynecological Association in 1914, in which eight cases were described of a type of bladder ulceration hitherto unreported.

The lesion is a chronic infiltration of all coats of the bladder wall, usually of broad extent in the vertex or free portion of the bladder, and presenting one or more minute superficial ulcers in the mucosa layer.

The urine is always macroscopically clear but on carefully pipetting and centrifuging, one can find microscopically a few leukocytes and a few erythrocytes. Culture of the urine is always negative.

The symptoms are those of an intense and most painful cystitis, usually having extended over a period of many years, and being uninfluenced or only partially allayed by the usual methods of cystitis treatment.

In addition to the bladder pain, strangury, and frequency of voiding, there are often referred pains to the intestines, and especially to the rectum, to the lateral pelvis and hips, and down the thighs, and to the vagina and perineal region.

The etiology of this type of bladder inflammation is still a matter for investigation. In one of the 18 cases there was a history of a colon bacillus cystitis following an Alexander operation 18 years previously. With this exception, none of the cases could be traced to a past operation, catheterization, childbirth, or gonorrhea, the frequent forerunners of a chronic cystitis. The fact that many of the patients refer the beginning of their symptoms to childhood or early adult life makes one think of the possibility of a focal infection as the etiological factor. The fact that the lesion is found in the vertex or free portion of the bladder rather than in the base, where are found the chief blood and lymph connections, is probably an argument against the focal infection theory.

As stated above, cultures from the urine are always sterile. In several cases the fresh tissues taken at operation have been macerated and used for anaerobic cultures with uniformly negative results. Many slides have been prepared with various stains in an attempt to demonstrate microorganisms in the tissues, but with negative results.

The successful treatment of these cases depends upon a complete excision of the entire area of infiltration, and this often involves the major portion of the bladder. One is surprised after repeated careful cystoscopy, which usually reveals an apparently superficial inflammatory condition limited to a comparatively small portion of the vertex of the bladder, to find at operation a widespread edema of the bladder mucosa.

<sup>1</sup> Paper read in the Section on Obstetrics, Gynecology, and Abdominal Surgery at the sixty-eighth annual session of the American Medical Association in New York City, June 7, 1917.

subtended by thickening and infiltration of all coats of the bladder.

The excision must include the entire edema area, and the histologic study of the removed specimen shows that the chronic inflammation of the walls is coextensive with the area of edema. This explains the futility of local treatments.

The past failure of urologists to discover this lesion in spite of the patient's intense and persistent bladder symptoms has been due chiefly to three factors. First, careless urinary analyses have overlooked the few leukocytes and erythrocytes present in an otherwise normal urine. Seeing a macroscopically clear urine and failing to grow a culture has led to a careless and negative microscopic examination, or on finding

a few leukocytes and erythrocytes these have been dismissed as of no significance. Second, the minute and superficial character of the ulcer portion of the lesion has caused it to be entirely overlooked or its importance to be ignored. Third, the usual location of the lesion in the vertex or on the anterior wall back of the symphysis is the most difficult portion of the bladder to explore by either the Nitze or Kelly methods of cystoscopy.

The extra-vesical or referred pain phenomena have led to many errors of diagnosis, 9 of the 18 patients having had a total of 16 operations directed toward the relief of their symptoms. These operations were largely futile because of a failure to make a proper diagnosis.

## PROCEEDINGS OF SOCIETIES

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

DECEMBER 3, 1917

#### 1. Exhibition of a Case of Psoriasis. DR. LLOYD W. KETRON.

This case is presented to the Society because of the remarkable shape of the lesions. The patient is a young man, aged 29, and is engaged in work of a clerical nature. He has had psoriasis for four years. The disease has only once entirely disappeared from his body, remaining away for about four months. It was during the second attack that the lesions took on the unusual contour which they now present. During the first attack, they were of the discoid type.

At the present time (see photograph), the disease is rather widely disseminated over the entire body. The most striking lesion is a band on the left side, about an inch and a half wide, extending from beneath the axilla with a serpentine contour down to the pubic region. There is a similar band on the right side of the body. On the thighs, and back, some of the lesions, although much smaller, are also coiled in a snake-like manner. Besides this serpentine arrangement, there are a few lesions of the discoid, or guttate variety.

The usual types of psoriasis are the punctate, guttate, discoid, and irregularly shaped patches of larger size. Occasionally, there is an annular form, and sometimes, when the lesions coalesce, a gyrate configuration may result. I have, however, never seen lesions showing such a clear-cut serpentine contour, as the ones in the present case. According to the patient's history, these bands were formed from the confluence of round patches, which appeared in the lines which the present lesions have now assumed.

In answer to Dr. Brown's question as to the treatment of psoriasis; there is nothing radically new at the present time, that promises to be of special value. Chrysarobin ointment still seems to be our most efficient remedy. It is, however, very unpleasant for the patient to use, because it stains all the clothing, and frequently sets up a dermatitis on the normal skin.

The injection of autogenous serum was rather enthusiastically used for a while, but the work of Dr. Willock in our

department gave practically negative results. Interesting metabolic studies in psoriasis cases have been lately carried



on by Schamberg and his associates in Philadelphia. They have shown that there is a nitrogen retention, and have claimed good results in treatment by giving a low protein diet.



The X-ray is of very great value in cases which have just a few very persistent chronic patches of psoriasis. These patches usually respond very quickly to one or more suberythema doses.

## 2. The Use of Relaxation Incisions in Dealing with Extensive Unstable Scars. DR. JOHN STAGGE DAVIS.

*Introduction.*—The treatment of tightly stretched unstable scars, which frequently break down, has long been a source of worry to the surgeon and of distress to the patient.

This type of scar usually follows extensive deep burns or loss of tissue by trauma where the wound has been allowed to heal by the slow process of cicatrization, without the aid of skin-grafting or of plastic operation.

The original wounds are always large and usually involve the entire circumference of a part, such as the leg or thigh, or occasionally the calvarium. In other words, the scar surrounds and compresses the part.

Some of the scars are bluish red with fine superficial vessels; others are pale and seem to have little or no blood supply. Frequently there are superficial ulcers of various sizes scattered over the surface. The scars are as unstable as wet tissue paper and the slightest injury will start an ulcer that will take weeks to heal.

There is little resistance to trauma or infection, and an area that is healed, in a very short time and without any apparent cause, may break down entirely; or multiple ulcers may develop.

A number of these cases have come under my care, and for a long time gave me much trouble. After using many methods with little success, it occurred to me to try relaxation incisions and to graft the defects thus made.

*Technic.*—It is preferable that the area be entirely healed before the incisions are made, but in some instances where the cicatrization of the superficial ulcers has been extremely sluggish I have not waited for complete healing, but have operated as soon as the granulations have been brought into a healthy condition. Before operation in the unhealed cases, after the granulations have become healthy, the part is put up in a dressing kept wet with normal salt solution for 24 hours. The granulations are then painted with tincture of iodine and the surrounding scar is cleaned with ether and alcohol.

Not infrequently the relaxation incisions can be made after infiltration with a local anesthetic, such as Schleich's solution, or one-half per cent novocain. In other instances a general anesthetic is advisable, especially if large immediate Thiersch grafts are to be used to cover the defect.

On an arm or leg long incisions should be made, parallel to the long axis of the part, down to the deep fascia, or down to healthy tissue if the destruction has been deeper than the fascia. Three relaxation incisions are usually sufficient for a limb and result in gaping wounds.

*Remarks.*—The immediate spreading of each relaxation incision varies with the tightness of the scar. In some

instances it is as much as 2.5 to 3 inches at the center of the incision. The spread of the first incision is, of course, the widest.

After the tension has been relieved the appearance of the scar tissue between the incisions soon changes, and instead of retaining the thin, glossy, mottled look, the tissue seems to thicken and to acquire greater stability. This improvement is much more marked after a few days.

When the scar is stretched over a broad expanse of bone, such as the skull, as many horizontal incisions as may be necessary should be made down to the periosteum. The spread of relaxation incisions over bone is not so marked as over soft parts, and some undercutting may have to be done. In these cases the beneficial effect is more marked after a week or two, but in the end the result is very satisfactory.

In some cases of very long standing the tissue exposed by relaxation incisions has atrophied from pressure and lack of use and has such a poor blood supply that immediate grafting is unwise. In these cases it is advisable to wait for several days until the wounds are lined with granulation tissue and then to apply the grafts.

In other instances immediate grafting is justified, but this point must be determined at the time of the operation.

It is extraordinary to note the rapidity of healing of the superficial ulcers after the relaxation incisions are made.

I have used only small deep grafts and Thiersch grafts on the defects caused by the relaxation incisions. These grafts have been so far entirely satisfactory, however, that there seems to be no reason why grafts of whole-thickness skin should not be used in cases where this type of graft may be necessary.

There has been no recurrence of superficial ulceration in any case where the tension has been completely relieved by the method described above.

*Conclusions.*—By the use of relaxation incisions with immediate or subsequent skin grafting of the defects, large unstable scars can be firmly healed in a comparatively short time, and patients who have been incapacitated for many months can resume their usual occupations.

I have used this method on a number of cases, with uniform success, and feel that it is a rational procedure and well worth trying.

## 3. Observations on Bird Malaria and the Pathogenesis of Relapse in Human Malaria. LIEUT.-COLONEL EUGENE R. WILKINSON, Army Medical School, Washington, D. C.

Published in the March number of the BULLETIN.

DECEMBER 17, 1917

## 1. The Preparation of the U. S. Army Triple Typhoid Vaccine (Illustrated with Moving Pictures). MAJOR C. G. SNOW, Army Medical School, Washington, D. C.

To be published in a later number of the BULLETIN.

## 2. Recent Work on the Differentiation of the Paratyphoid Group in Relation to Disease in Man. DR. CHARLES KRUMWIEDT, Department of Health, New York City.

## DISCUSSION

DR. W. W. FORD.—Of course it is very gratifying to me to find that a distinction between the various types of paratyphoid bacilli made out so many years ago has been confirmed by Dr. Krumwiede in a manner which is more comprehensive than that shown in the original suggestion.

There are many extremely interesting features about this group. In the original work upon the paratyphoid organisms, I was impressed by the fact that practically all of the paratyphoid cultures rendered milk alkaline if you gave them sufficient time to act. That is to say, the old distinction between paratyphoid A and B, based upon the production

of permanent acidity in milk in the one group, and the loss of acidity and production of alkalinity in the other, was not a valid distinction. The two groups could be differentiated, however, by the use of the higher polysaccharids, such as arabinose and xylose. One reason for the reported stability of *Bacillus enteritidis* of Gärtner is that so few cultures of this organism are available for study. The majority of those found in America for instance, are derived from a culture sent to The Johns Hopkins many years ago by Dr. Durham, of Cambridge, England. It is interesting to note how Dr. Krumwiede's studies have enabled bacteriologists to trace the origin of many of these strains back to their original animal host.

## BOOKS RECEIVED

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- A Text-Book of Anatomy for Nurses.* By William Gay Christian, M. D. With 34 original illustrations, 5 of which are in colors. 1917. 12°. 222 pages. C. V. Mosby Company, St. Louis.
- Fiske Fund Prize Essay No. LVII. The Role of the Teeth and Tonsils in the Causation of Arthritis.* By Dr. Joseph F. Hawkins. 1917. 8°. 29 pages. Snow & Farnham Co., Providence, R. I.
- The Child in Health and Illness.* By Carl G. Leo-Wolf, M. D. Illustrated. 1917. 8°. 297 pages. George H. Doran Company, New York.
- Royal Academy of Medicine in Ireland. Transactions. Volume XXXV.* Edited by J. Alfred Scott, M. A., M. D., F. R. C. S. I. 1917. 8°. 292 pages. John Falconer, Dublin.
- The Institutional Care of the Insane in the United States and Canada.* By Henry M. Hurd, William F. Drewry, Richard Dewey, Charles W. Pilgrim, G. Alder Blumer and T. J. W. Burgess. Edited by Henry M. Hurd, M. D., LL. D. Volumes III and IV. 1916-1917. 8°. 880 pages; 652 pages. The Johns Hopkins Press, Baltimore, Md.
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- The Prescription, Therapeutically, Pharmaceutically, Grammatically and Historically Considered.* By Otto A. Wall, Ph. G., M. D. Fourth and revised edition. 1917. 8°. 274 pages. C. V. Mosby Company, St. Louis.
- Diseases of the Skin.* By Richard L. Sutton, M. D. With 833 illustrations and 8 colored plates. Second edition, revised and enlarged. 1917. 8°. 1021 pages. C. V. Mosby Company, St. Louis.
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- Radium Therapy in Cancer at the Memorial Hospital, New York. (First Report: 1915-1916.)* By Henry H. Janeway, M. D. With the discussion of treatment of cancer of the bladder and prostate, by Benjamin S. Barringer, M. D., and an introduction upon the physics of radium, by Gioacchino Failla, R. E., A. M. 1917. 8°. 242 pages. Paul B. Hoeber, New York.
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*Royal College of Surgeons of England. Calendar.* 1917. 8°. 407 pages. Taylor & Francis, London.

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*Studies from the Rockefeller Institute for Medical Research.* Reprints. Volume XXVII. 1917. 8°. 559 pages. The Rockefeller Institute for Medical Research, New York.

*A Text-Book of War Nursing.* By Violetta Thurstan. 1917. 12°. 227 pages. G. P. Putnam's Sons, London and New York.

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*Surgery and Diseases of the Mouth and Jaws.* A Practical Treatise on the Surgery and Diseases of the Mouth and Allied Structures. By Vilray Papin Blair, A. M., M. D., F. A. C. S. Third edition, revised so as to incorporate the latest war data concerning gunshot injuries of the face and jaws. With 460 illustrations. 1917. 8°. 733 pages. C. V. Mosby Company, St. Louis.

*The Medical Association of the State of Alabama. Transactions.* 1917. 8°. 632 pages. The Brown Printing Company, Montgomery, Ala.

## NEW PUBLICATIONS.

The following six monographs:

*Free Thrombi and Ball-Thrombi in the Heart.* By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

*Benzol as a Leucotoxin.* By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

*Primary Carcinoma of the Liver.* By M. C. WINTERITZ, M. D. 42 pages. Price, 75 cents.

*The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911.* By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

*The Origin and Development of the Lymphatic System.* By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

*The Nuclei Tuberos Laterales and the So-called Ganglion Opticum Basale.* By EDWARD F. MALONE, M. D. Price, \$1.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

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## THE RESULTS OF TREATMENT IN PERNICIOUS ANEMIA

By ARTHUR BLOOMFIELD, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital)

The treatment of pernicious anemia, generally employed until a few years ago, consisted of a regimen in which rest, special diet, and the administration of arsenic were the principal features. Recently more radical measures have come into prominence, namely, transfusion of blood, splenectomy, and operations for the elimination of "foci of infection." The reports on these newer methods have dealt so far mainly with general considerations and immediate results:

Ottenberg and Libman<sup>1</sup> state that transfusion leads to remission in about one-half of the cases. Archibald<sup>2</sup> found that of 26 patients who received transfusions 69 per cent derived marked immediate benefit. Larrabee<sup>3</sup> from a small experience (six cases), and Barker and Sprunt<sup>4</sup> feel that if the anemia is severe and progressive and responds poorly to other methods transfusion should be tried. Meleney and his associates,<sup>5</sup> without making detailed statements, conclude that transfusion is of real value in pernicious anemia, spontaneous remissions having been hastened in many cases by the procedure. With regard to splenectomy Lee, Vincent, and Robertson<sup>6</sup> found in a series of five cases that the immediate result was prompt post-operative recovery and a definite remission of the disease. Krumbhaar,<sup>7</sup> in a review of the late results of splenectomy in 153 cases, noted a post-operative mortality of about 20 per cent and also that the improvement was transient in most of the patients. Minot and Lee<sup>8</sup> emphasize the importance of careful selection of cases. Their report includes a thorough study of immediate and late results of transfusion and splenectomy in a somewhat larger series. They find that these measures, when properly employed, offer more than other methods of treatment alone, although they may fail in individual cases.

A recent report by Giffin<sup>9</sup> states that splenectomy does not cure pernicious anemia but that there is considerable improvement in more than half of the cases, especially when the procedure is combined with transfusion. William Hunter first emphasized the relation of "oral sepsis" to severe anemias, and recently Barker and Sprunt<sup>4</sup> have laid stress on the importance of eliminating "foci of infection" in the treatment of pernicious anemia.

Inasmuch as these procedures are elaborate, and at times not without immediate ill effects, it seems important to have more information as to their value in prolonging life or inducing remissions. In this report a series of 57 cases has been analyzed in detail with particular reference to the comparative value of the various methods of treatment. All the patients were studied in the Medical Clinic of The Johns Hopkins Hospital and were selected serially from the records of the past five years. In every instance the history, physical findings, and the blood picture were typical of the so-called idiopathic type of pernicious anemia.

Determination of the value of therapy in this disease is notably difficult owing to certain features belonging to the natural course of the malady. The following possible criteria suggest themselves:

1. *The Effect of Treatment on the Total Duration of the Disease.*—This should be the most useful guide. It must be remembered, however, that the actual onset cannot be determined, and in only four-fifths of this series was there a clear history as to the beginning of symptoms. Furthermore, some of the cases run a rapidly progressive course, whereas others show repeated remissions. As a rule, the patient is under

close observation only during the relapses, and the care which he takes of himself at other times may influence the course of the disease. Thus the reappearance of symptoms has been noted not infrequently after exposure, shock, or over-exertion. Finally, the advantage of studying large series of hospital cases is to some extent offset by the difficulty of tracing many of these patients.

2. *The Readiness with which Remission is Induced.*—This furnishes a doubtful standard of treatment, since spontaneous remissions may occur at any time even when the blood count has been very low, or after the condition has been stationary under observation for several weeks or even months. Furthermore, remissions usually occur more readily in the earlier stages of the disease than later; in fact in every case there eventually comes a period when all measures are unavailing and the downward course is unarrested. This is illustrated by the cases of several patients in this series who returned to the hospital at intervals and finally became totally refractory to the measures that seemed before to produce striking results.

3. *The Length of the Remission.*—This is often difficult to determine. It may vary spontaneously, and depends to some extent on the conduct of the patient after leaving the immediate care of the physician.

4. *The Effect of a Particular Form of Therapy on Special Symptoms* is difficult to estimate.—Fever, gastro-intestinal disturbances, and the symptoms referable to the anemia itself tend to clear up as the remission sets in and the blood improves. The spinal cord disturbances on the other hand are notably but little affected by any therapy, and may even progress at a time when the condition seems to be improving in other ways. Gain in weight does not always run parallel with improvement in the blood count and general condition. The degree of the remission, with reference to the gain in blood, may furnish some standard of the effect of therapy.

5. *The death rate in the hospital* offers a means of comparing the value of therapeutic measures, but often the patient is in a late stage of the disease refractory to any treatment.

6. *The Character of the Blood Picture.*—Minot and Lee<sup>8</sup> recently report morphological blood studies in pernicious anemia which may turn out to be of aid in prognosis and in estimating therapeutic effect, but since gain or loss of blood elements depends on the balance of blood destruction and blood formation, patients showing the most active signs of regeneration may be doing badly, whereas others may gain rapidly without evidence in the peripheral blood of marked marrow stimulation.

Very little information is at hand about the immediate effect of transfusion or splenectomy on the blood picture. Lee, Minot and Vincent<sup>10</sup> find immediate stimulation of the bone marrow following splenectomy, and Meleney<sup>8</sup> has noted a leucocytosis shortly after transfusion.

It is clear that no single standard of therapeutic effect is reliable. In this report, therefore, the cases have been analyzed from these various points of view.

## RESULTS OF GENERAL TREATMENT

Twenty-eight cases were treated by the older methods consisting essentially of rest in bed, diet, hydrochloric acid, and arsenic. The results of such therapy are well known and these patients are included mainly as controls to compare with those who had transfusion or splenectomy, or in whom foci of infection were eliminated. A few points may, however, be emphasized. Absolute rest in bed over considerable periods of time is certainly the most important feature of this regimen. Arsenic and hydrochloric acid are apparently useless, unless the patient is kept quiet at the same time, and cessation of improvement or relapse has occurred not uncommonly as soon as active life was resumed, despite continued drug therapy. Furthermore, it often appears on going back into the history of the period of the disease before the patient was under medical care that the "weakness and shortness of breath" were relieved by a few weeks of rest in bed. The value of arsenic is based entirely on general impressions. It was used in every instance in this series either in the form of Fowler's solution, sodium cacodylate, or salvarsan. Analysis of the cases, however, yields no data of value as to its efficacy. Achlorhydria gastrica was uniformly present and hydrochloric acid was given usually both before and after meals. In a few instances gastro-intestinal disturbances, especially diarrhoea, seemed to be relieved, but in most of the patients these symptoms disappeared quite rapidly with the progress of the remission apparently regardless of any symptomatic therapy. In about one-half of the cases there were accurate statements as to loss of weight. This usually amounted to from 10 to 50 pounds from the onset of symptoms to the time of admission to the hospital. Unless special features of the case made feeding impossible, a liberal diet was allowed. No special dietary regimen or restriction of any food element was attempted. No relation between gain in weight and improvement in the blood or general condition is apparent in this series. Of 33 cases in which there was clinical improvement, and the weight on admission and discharge was recorded, 22 gained and 11 lost. The examples in Table I illustrate that gain in blood does not

TABLE I

Patient	Blood count on admission	%	Blood count on discharge	%	Days in hospital	Weight on admission in pounds	Weight on discharge in pounds	Loss or gain in pounds
Hu....	2,400,000	50	3,300,000	76	78	151	135	16
H....	1,300,000	20	3,400,000	60	40	133	127	6
B....	1,100,000	27	4,000,000	62	51	130	118	12
P....	1,130,000	26	3,100,000	60	48	174	164	10
G....	1,400,000	43	3,000,000	60	35	91	81	10
S....	800,000	22	2,200,000	47	85	93	91	2

necessarily go hand in hand with gain in weight. After a remission is established and digestive disturbances have cleared up, rapid gain in weight usually occurs.

## TRANSFUSION

Twenty-six patients received transfusions of blood varying in number from 1 to 17. The largest amount of blood given to one patient was 8700 cc., the smallest amount was 300 cc. The

single transfusions varied in amount from 300 to 900 cc. The citrate method and the Lindeman syringe method were used most often; in a few cases indirect transfusions of defibrinated blood were given, and in one case direct transfusion was used as a preliminary to splenectomy. The technique employed has been described recently by McClure and Dunn," and by Sydenstricker, Mason and Rivers" from this clinic, and will not be repeated.

The therapeutic effect of transfusion in pernicious anemia may be discussed under several heads.

1. *The Value of Transfusion as an Emergency Measure.*—Quite apart from any ultimate effect the question arises whether transfusion may tide over a patient during an unusually severe relapse, or may check further fall of the blood count where this is very low. To illuminate this point the following mortality statistics are presented. Three hundred and sixty-three patients with pernicious anemia have been treated in The Johns Hopkins Hospital, of whom 58, or 16 per cent, died in the wards. Of the 31 who received transfusion 6, or 19 per cent, died, whereas of the 332 who did not receive transfusion 52, or 15.5 per cent, died. Of the 57 cases studied in this report, 26 were given transfusions with 6 deaths in the hospital—23 per cent. Of the 22 cases not transfused and receiving only general therapy, 5, or 22.7 per cent, died. Some of the patients were admitted to the hospital several times. The patients who were given transfusions had 37 admissions with 6 deaths, or 16.2 per cent; those not transfused had 28 admissions with 5 deaths, or 17.8 per cent. The cases have been divided further into those entering with counts of less than 1,000,000 red cells, and those with counts of over 1,000,000 red cells. Patients not receiving transfusion were admitted 10 times with counts of less than 1,000,000, and 18 times with counts of over 1,000,000. Two of the former—20 per cent—died; 3 of the latter, or 17 per cent. Of the 37 receiving transfusions 9 entered with counts of under 1,000,000 of whom 3, or 33.3 per cent, died; of the 28 with counts over 1,000,000, 3, or 33.3 per cent, died; of the 28 with counts over 1,000,000, 3, or 10.7 per cent, died.

These figures, therefore (Table II), furnish no evidence that transfusion was of value as an emergency measure, or that the immediate mortality was decreased by the procedure.

TABLE II

Cases receiving transfusion				Cases not receiving transfusion		
	Number	Deaths		Number	Deaths	
		Number	Per cent		Number	Per cent
Total cases.....	26	6	23.0	22	5	22.7
Total admissions.....	37	6	16.2	28	5	17.8
Cases with counts under 1,000,000.....	9	3	33.3	10	2	20.0
Cases with counts over 1 000,000.....	28	3	10.7	18	3	17.0

2. *The Immediate Effect of Transfusion.*—Following the injection of 500 cc. or more of blood there was usually an immediate increase in the blood count and hemoglobin. Rises

of as much as 1,000,000 cells and 15 per cent of hemoglobin were frequently noted. In most cases there was a subsequent fall. Counts were not made often enough to distinguish the purely mechanical result of transfusion from later reactive effects. This question is now being studied in detail. Subjective improvement was often striking, the patient saying he felt better while the blood was being injected. Quite possibly this was in some cases a psychic effect.

3. *The Relation of the Onset and Degree of Remission to Transfusion.*—The cases were studied to find out if remission occurred sooner and more often in patients receiving transfusion than in others. For the purpose of this discussion a remission is regarded as including marked general and symptomatic improvement with a gain of at least 1,000,000 red cells or 20 per cent of hemoglobin. Among the patients who were not transfused remission set in in the hospital 8 times in 28 admissions, a percentage of 28.5; in the patients given transfusion there were 19 remissions in 37 admissions, or 51 per cent. The number of days in the hospital until the highest blood count was reached averaged 43 in the untransfused patients, and 43 in those receiving blood. The maximal count was reached on an average of 34 days after the first transfusion.

The degree of the remission as measured by gain in blood was also studied in the two groups. Counts of 4,000,000 or over were reached in 4 cases of the group receiving blood, counts of 3,000,000 to 4,000,000 in 9, and counts of 2,000,000 to 3,000,000 in the remaining 6. Counts of 4,000,000 or over were reached only once in the patients who were not transfused, counts of 3,000,000 to 4,000,000, only twice, the remaining 5 patients reaching counts of from 2,000,000 to 3,000,000. Gains of over 3,000,000 cells were made in 4 patients receiving transfusion, gains of 2,000,000 to 3,000,000 in 6, and gains of 1,000,000 to 2,000,000 in 9. The largest gain in the patients who were not transfused was 3,000,000 in one instance, another gained 2,000,000 cells, 4 gained from 1,000,000 to 2,000,000 cells, and 2 gained less than 1,000,000 cells and but 22 per cent and 30 per cent of hemoglobin respectively. These facts are summarized in Table III.

TABLE III

Patients receiving transfusion				Patients not receiving transfusion			
Number of admissions	Remissions			Number of admissions	Remissions		
	Number	Per cent	Days		Number	Per cent	Days
37	19	51	43	28	8	28.5	43
Reaching counts of		Number	Per cent	Reaching counts of		Number	Per cent
4,000,000 or over....		4	21	4,000,000 or over....		1	12.5
3,000,000 to 4,000,000		9	47	3,000,000 to 4,000,000		2	25.0
2,000,000 to 3,000,000		6	32	2,000,000 to 3,000,000		5	62.5
Gains of		Number	Per cent	Gains of		Number	Per cent
3,000,000 or over....		4	21	3,000,000 or over....		1	12.5
2,000,000 to 3,000,000		6	32	2,000,000 to 3,000,000		1	12.5
1,000,000 to 2,000,000		9	47	1,000,000 to 2,000,000 or 20% Hb.		6	75.0



The relation of gain in blood to the amount of blood given is shown in Table IV.

TABLE IV

Patient and number of admission	Number of transfusions	Amount of blood given c. c.	Gain in blood (R. B. C.)	Days from admission	Days from first transfusion	Duration of symptoms on admission (approxim.)
B. 1.....	5	4400	3,000,000	38	23	10 mos.
P. 1.....	6	3120	3,500,000	37	29	12 "
Pr. 1.....	6	2980	2,200,000	34	25	12 "
P. 3.....	6	2850	2,300,000	43	38	18 "
H. 1.....	5	2770	1,400,000	36	26	?
R. 2.....	3	2500	2,300,000	13	9	12 "
Bu. 1.....	5	2300	1,500,000	34	24	12 "
Bu. 2.....	5	2220	2,100,000	27	23	18 "
S.....	4	1650	1,400,000	83	73	12 "
E.....	4	1500	3,000,000	35	34	?
M. 1.....	3	1500	2,200,000	31	29	12 "
A. 1.....	2	1450	1,000,000	52	47	9 "
Bu. 3.....	4	1400	1,100,000	31	25	24 "
Pr. 2.....	3	1325	900,000	93	91	24 "
Mur.....	3	1300	600,000	132	88	3 yrs. ?
S. 1.....	4	1160	1,600,000	35	25	?
M. 2.....	3	1150	400,000	35	33	18 mos.
O.....	3	920	500,000	60	58	24 "
H.....	2	800	2,100,000	40	33	8 "
W.....	1	750	300,000	17	3	?
Bre.....	1	650	100,000	45	1	?
M.....	1	630	400,000	23	4	8 "
Bi.....	2	600	3,300,000	90	89	1 "
C.....	2	550	1,800,000	42	35	?
Wad.....	1	375	1,000,000	56	37	12 "
Be.....	1	250	600,000	36	29	8 "
H. 2.....	5	3500	Died, second. lues, pneumonia.	18	?	?
B. 3.....	3	1600	Died, coma.	48	?	?
Horn.....	3	1000	Died, coma.	24	?	?
P. 4.....	3	420	Died, coma.	8	?	?
Ha.....	1	300	Died, coma.	12	?	?
Mu.....	1	300	Died, edema of lungs.	12	?	?

From this table it appears that the patients receiving most blood in general made the greatest gains. Thus, of the 10 gaining 2,000,000 or more cells, 8 received 3 or more transfusions with a total of 1500 cc. or more of blood. None of the 5 receiving only one transfusion of less than 1000 cc. gained over 1,000,000 cells. Of the 19 cases regarded as having a remission all but one received more than one transfusion and all but 5 received 1400 cc. or more of blood.

The success of transfusion seems to depend also on the stage of the disease. Where the previous duration of symptoms could be clearly determined in the patients showing a remission it was found to be 12 months or less in 10 instances, 18 months in 2, and 24 months in 1 case. The importance of the stage of the disease is further illustrated by transfusion results in the same patients on repeated admissions to the hospital (Table V).

In summary, then, it seems that in patients who are not in a stage of the disease refractory to any form of treatment, remission has come on more often when transfusion has been performed. Furthermore, the amount of blood gained runs roughly parallel to the number of transfusions and the total amount of blood given. It seems rational, therefore, if transfusion is done at all, to be prepared to inject blood repeatedly if the patient shows a tendency to respond. Single transfusions in cases refractory to other therapy led to no improvement in this series.

4. *The Length of the Remission.*—It was possible to determine accurately the length of the remission following trans-

TABLE V

Patient and number of admission	Number of transfusions	Amount of blood given c. c.	Gain in blood (R. B. C.)	Days from admission	Days from first transfusion	Duration of symptoms on admission (approxim.)
B. 1.....	5	4400	3,000,000	38	23	10 mos.
*B. 2.....	3	2500	2,300,000	13	9	12 "
B. 3.....	3	1600	severe reactions to homologous blood; death.			18 "
*P. 1.....	6	3150	3,500,000	37	29	12 "
P. 2.....	5	2300	800,000 (34% Hb.)	49	47	14 "
P. 3.....	6	2850	2,300,000	43	38	18 "
P. 4.....	3	420	severe reactions to homologous blood; death.			24 "
Bu. 1.....	5	2300	1,500,000	34	24	12 "
Bu. 2.....	5	2200	2,100,000	27	23	18 "
Bu. 3.....	4	1400	1,100,000	31	25	24 "
M. 1.....	3	1500	2,200,000	31	29	12 "
M. 2.....	3	1150	400,000	35	33	18 "
Pr. 1.....	6	2980	2,200,000	34	25	12 "
Pr. 2.....	3	1325	900,000	93	91	24 "

\* Splenectomy.

fusion in 13 instances. The return of symptoms with a fall in the blood count was regarded as indicating the onset of relapse. These data are summarized in Table VI.

TABLE VI

Patient and number of admission	Amount of blood given c. c.	Duration of symptoms at time of remission	Duration of remission	Previous remissions	Subsequent remissions
B. 1.....	4400	10 mos.	2 wks.	0	
Pr. 1.....	2980	12 "	10 mos.	0?	1
Bu. 1.....	2300	12 "	6 wks.	0	3
Bu. 2.....	2200	18 "	4 mos.	1	2
Bu. 3.....	1400	24 "	4 wks.	2	1
Bu. 4.....	1500?	28 "	4 wks.	3	0
M. 1.....	1500	12 "	4 mos.	2	0
A. 1.....	1450	9 "	21 "	0	0
Pr. 2.....	1325	24 "	4 "	1	
G.....	1160	?	20 "	+	0
H.....	800	6 "	7 "	+	0
C.....	600	3 yrs.	5 "	?	0
Bi.....	550	2 wks.	8 "	0	0

These cases do not indicate that transfusion led to prolongation of the remission. In only three instances did it last over six months, whereas among 329 cases collected by Cabot<sup>12</sup> there were remissions of over six months in 165. No relation between the amount of blood given and the duration of the remission is apparent.

5. *The Duration of Life.* Thirteen of the patients receiving transfusion are now dead, four are alive, while the remainder could not be traced. The total individual duration of life from the onset of symptoms was as shown in Table VII.

Although this series is too small to serve as a basis for group percentages it is clear that there was no demonstrable prolongation of life in the cases in which transfusion was employed. Patients treated by the older general methods frequently live four years or longer. Thus, in 647 cases Cabot<sup>12</sup> found 79 patients who lived over four years. Furthermore, it is noteworthy in this series that the patients living longest were not the ones in whom remission followed transfusion.

Four patients are still alive. The symptoms have been present one, two, two, and four years respectively.

TABLE VII

Patient	Duration of life from onset of symptoms	Remission after transfusion
H. ....	4 yrs.	None.
W. ....	4 "	None.
H. ....	3½ "	None.
C. ....	3½ "	Remission.
O. ....	3½ "	Remission.
M. ....	2 "	Remission.
D. ....	1½ "	None.
H. ....	1½ "	Remission.
M. ....	1½ "	Remission.
B. ....	1 "	Remission.
M. ....	1 "	None.
M. ....	10 mos.	None.
H. ....	8 "	None.

6. *The Effect of Transfusion on Symptoms.*—An analysis of the course of symptoms shows no definite variation in the groups of cases treated by different methods. In general, with

one, death from pulmonary embolus occurred 19 days after operation. Six of the remaining patients are dead. The data in these cases are summarized in Table VIII.

In no case was the clinical picture essentially altered, and no unusual prolongation of life occurred. Thus one patient lived two and a half years after splenectomy, and another is alive after one and a half years but very ill with recurring femoral phlebitis. In five cases transfusions were given during the period immediately following splenectomy. None the less in the four cases in which the length of the remission could be accurately determined symptoms returned after periods of three, four, four, and eight months, respectively. In one case there was no remission but progressive failure, in another post-operative death occurred from pulmonary embolus. The other two patients did not have the relapsing type of the disease. The height of the blood count cannot be regarded as remarkable, inasmuch as the patients were transfused after operation except those not of the relapsing type. These cases fail to bear out the view that transfusions are "held" better after splenec-

TABLE VIII

Patient	Age	Duration of symptoms at time of splenectomy	Blood at time of splenectomy			Previous remissions	Previous transfusions		Maximal blood count after splenectomy	Days	Length of remission	Transfusion after splenectomy		Total duration of life from onset of symptoms	Duration of life after splenectomy	Remarks		
			%	No.	c. c.		%	No.				c. c.						
W.	35	1 year.	1,700,000	3,600	27	?	1	375	3,500,000	10,400	70	60	8 mos.	"	"	4½ yrs. 2½ yrs.	Three subsequent remissions. Death from acute dysentery.	
P...	62	1 "	4,000,000	1,400	65	1	6	3120	4,700,000	4,600	84	32	3 "	11	5200	2 "	11 mos.	Rapidly progressive cord changes. Death in coma.
B...	43	8 mos.	3,400,000	.....	60	1	8	5988	3,800,000	6,000	72	42	3 "	5	2300	19 mos. 7 "	"	Death in coma.
A...	38	14 "	1,800,000	3,000	35	1	5	3475	4,900,000	4,900	90	74	4 "	7	5000	2½ yrs. 16 "	"	Death in coma after rapid relapse.
Bo.	55	10 "	2,800,000	5,300	93	?	0	....	3,900,000	6,800	100	45	Disease not of relapsing type.	1	400	29 mos. 19 "	"	Progressive cord changes. Death in coma after rapid relapse.
S...	25	1½ yrs.?	3,100,000	3,000	87	?	0	....	4,200,000	8,400	102	..	Disease not of relapsing type.	0	....	3 yrs. (alive)	1½ yrs. (alive)	Patient still living.
H...	57	3 "	2,900,000	10,400	58	?	5	2770	2,100,000	.....	31	..	No remission.	6	4000	3½ yrs. 5 mos.	"	Rapidly progressive anemia. Pneumonia, death.
C...	42	5 mos.	3,500,000	7,000	91	?	0	....	.....	.....	..	.....	0	....	6 mos. 20 dys.	"	Death, pulmonary embolus.	

\* Direct transfusion at time of splenectomy

the improvement in the blood, the symptoms referable to the anemia itself (dyspnoea, palpitation, dizziness, and weakness), and the gastro-intestinal disturbances were alleviated or disappeared. Fever regularly tended to fall and was rarely present on discharge in the patients who did well otherwise. Absence of relief of the central nervous system symptoms during the remission is well known. It was striking that transfusion also was ineffective in removing these disturbances. The disappointment of the patients was uniform in this regard, although in a few instances there was perhaps slight improvement.

#### SPLENECTOMY

Although splenectomy for pernicious anemia is no longer done in this clinic, it seems of interest to report the late results. The operation was performed in 8 instances. In

only one, death from pulmonary embolus occurred 19 days after operation. Six of the remaining patients are dead. The data in these cases are summarized in Table VIII. In no case was the clinical picture essentially altered, and no unusual prolongation of life occurred. Thus one patient lived two and a half years after splenectomy, and another is alive after one and a half years but very ill with recurring femoral phlebitis. In five cases transfusions were given during the period immediately following splenectomy. None the less in the four cases in which the length of the remission could be accurately determined symptoms returned after periods of three, four, four, and eight months, respectively. In one case there was no remission but progressive failure, in another post-operative death occurred from pulmonary embolus. The other two patients did not have the relapsing type of the disease. The height of the blood count cannot be regarded as remarkable, inasmuch as the patients were transfused after operation except those not of the relapsing type. These cases fail to bear out the view that transfusions are "held" better after splenec-

rest, diet, arsenic, and hydrochloric acid. Splenectomy was then performed. This patient's blood has remained fairly high ever since. He is alive after one and a half years.

In summary, these cases furnish no proof that life was prolonged, that remission was longer and more marked, that transfusions were better "held," or that there was any special relief of symptoms following splenectomy.

#### ELIMINATION OF "FOCAL INFECTIONS"

Since the work of William Hunter, many writers have ascribed the picture of pernicious anemia to local "foci of infection." This doctrine has come especially to the front in the last few years largely owing to the studies of Billings\* and his co-workers. That the association of these foci with pernicious anemia is a causal one is not, however, as yet proved. It seems that one should be very cautious in assuming an etiological relationship between a disease picture so clear cut and running such a typical course as pernicious anemia and lesions of such frequent occurrence as periapical abscesses, infected tonsils, and other local "foci of infection." The anemias known to be due to infection such as those occurring in septic diseases are of the simple secondary type and clear up when the primary disease heals or is eliminated. It may be that less definite deleterious effects are exercised on the course of the disease by foci of infection without specific causal relationship.

In 12 cases a thorough study of the nose, throat, sinuses, teeth, gastro-intestinal tract, and lower urinary tract was made for foci of infection and, when found, these were eliminated. All these patients finally received clean bills of health from the various specialists. Most of them were given transfusions and in one case splenectomy was also performed. In none was there any feature in the subsequent course to distinguish them from the group in which foci were not found, or if found were not treated, either as to total duration of life or extent and degree of remission.

It is unlikely, therefore, that such foci of infection are the cause of pernicious anemia, although it seems wise to treat them for their own sake as well as for any possible general beneficial effects which may follow.

#### CONCLUSIONS

An effort has been made to analyze the results of treatment in these cases from a purely objective point of view. Clinical

impressions have been disregarded, and no attempt has been made to promote or discredit any particular therapeutic measure. It should be recognized that such statistics lead to only general conclusions which allow of exceptions in individual cases. The results may be summarized as follows:

1. No definite evidence has been found that either transfusion, splenectomy, or elimination of foci of infection prolongs the life of patients suffering from pernicious anemia.

2. Transfusion performed at a time when the patient was not refractory brought on remission in about half the cases, and enabled the blood count to be raised to a higher level than it reaches in cases not so treated.

3. Such artificial plethoras did not increase the duration of the remission, although the patients usually had a sense of well being while the count was high.

4. At other times the same patients were refractory to transfusion as well as to other methods of treatment.

5. The central nervous system symptoms were as little benefited by transfusion and splenectomy as by other methods of therapy.

6. Transfusions of blood were not "held" better after splenectomy than before.

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## TOBACCO SMOKE AND PULMONARY TUBERCULOSIS\*

By ALLEN K. KRAUSE

This study\* may strike many as having turned out "against the rule." But to some of us its results are not unexpected. Major Webb finds, in effect, that comparatively few non-

smokers (only 27 per cent) have ronchi, while most smokers do exhibit these signs of chronic bronchial irritation, and cigarette smoke inhalers almost invariably show them (83 per cent). He finds further that of a comparatively large body of young men (over 3000), the proportion that was discharged from active army service because of active tuberculosis was no higher among the smokers, the men who had ronchi, than among the non-smokers with relatively "quiet" chests.

\*Elaboration of remarks made in a discussion of a paper, "The Effect of the Inhalation of Cigarette Smoke on the Lungs. A Clinical Study," read by Major Gerald B. Webb before the Laennec Society of The Johns Hopkins Hospital, February 25, 1918.



Ronchi are indications of bronchial irritation and a consequent inflammation; and it might have been predicted that individuals who are habitually subjecting their respiratory tract to the far-from-soothing influence of cigarette smoke would be more likely to exhibit its effects, that is, inflammation, than those whose gaseous intake is confined to the more or less undefiled atmospheric air of town and country. This side of Major Webb's study represents, therefore, no startling discovery. But its other result—that the “ronchous” smoker's acquaintance with the tubercle bacillus is just as favorable and just as well guarded as that of his non-smoking neighbor—embodies certain implications that run so counter to what we have been taught and what we have comfortably believed, that it perhaps deserves a little more than a word of notice.

We were once told that in our struggle against the tubercle bacillus it was of great importance that we avoid anything that would bring about irritation of the respiratory tract. I believe that much of the antituberculosis propaganda still recites that inflamed conditions of the nose, throat, larynx and bronchi lay us more open to tuberculous infection. The old admonitions had it that the inflammations brought about by the common cold, catarrh, tobacco, etc., left us in a “run down” condition and therefore comparatively defenseless against bacillary invasion. The idea undoubtedly had its birth in the long-noted and indisputable fact that the common cold and other catarrhal conditions were frequently followed by outbreaks of pulmonary tuberculosis. Therefore, the local inflammation was favorable and nourishing soil for the implantation of tubercle bacilli and a host of other microorganisms. This was a very natural presumption. For an inflamed tissue is a diseased tissue and without examining the matter more closely it seems reasonable to presuppose that a diseased tissue is more open to infection—to bacterial implantation and invasion—than a healthy tissue.

But let us analyze these matters further. In another place I<sup>1</sup> have already pointed out that it is at least debatable whether inflammation leads to increased susceptibility to bacterial infection. Clinical data at once belie this assumption. If the proposition is maintained, then I would at once ask questions something as follows: Why are chronic leg ulcers so uncommonly the seat of acute bacterial infection? Why is erysipelas more often seen to arise in the healthy non-inflamed skin or in the clean, operative wound than in the epithelioma ulcer or in the open patch of lupus where we should look for it? Why is a story of frank, acute bronchitis ushering in acute lobar pneumonia unusual?

In this connection too I have elsewhere called attention to what Opie<sup>2</sup> has to say on the function of inflammation. “Views concerning the nature of inflammation,” he writes, “are widely diverse, but all are agreed that inflammation accomplishes the destruction and solution of a variety of substances, and notably those proteins which form the bodies of parasitic invaders.” In the same lecture Opie cites experimental evidence as follows: “Pawlowsky has demonstrated the presence of staphylococci in the blood and organs of guinea-pigs from 24 to 48 hours after inoculation of the knee-

joint, but has been able to show that dissemination is inhibited or wholly prevented if, before inoculation, acute inflammation of the joint has been produced by the injection of some sterile irritant, such as turpentine, alcohol or solution of quinine.” And again, “Issayeff . . . showed that the peritonitis induced by a variety of sterile irritants, such as a foreign blood serum, bouillon, or normal salt solution, temporarily increases resistance to subsequent intraperitoneal inoculation of bacteria.”

Now what does all this mean? It must at least suggest that inflammation is the visible expression of an animal organism's capacity to react to irritation (whether the irritation be mechanical, chemical or thermal; whether it be set up by organized or unorganized material, by inert or living substances, by grains of sand or bacterial parasites), and that this reacting capacity is a true resisting function of tissues. It is an effort on the part of tissue to defend itself, to limit the assault of the invader, to wall off the offending irritant. If this be true—and to me it hardly admits of any doubt—we must give up our ideas that inflamed tissues are especially favorable soil for bacterial invasion. They are the very reverse: they are points of unusual resistance.

It would be perfectly useless to speculate as to what element in the inflammatory process brings into the struggle the resisting units or substances—as to whether the serum, or the leucocytes, or the new proliferation of fixed cells renders the invaders impotent. That is material for studies of another nature. The point I want to make here is that the animal body interposes a something, a barrier, if you will, between itself and parasites that are trying to gain a foothold; and that the subsequent fate of the animal will depend largely on the competence and integrity of this barrier. In what this competence consists is another matter that is not at present germane.

It is because of considerations like these that some of us have begun to doubt the soundness of the view that looks upon an inflamed spot as a *locus minoris resistentiæ* for infection by microorganisms. But what we have to say applies only to the incident of *becoming infected*, not to what may or may not happen to a focus of infection that is already established.

It seems to me that it is not sufficiently well recognized, or, at least, not emphasized enough, that the factors that favor or prevent the implantation of an infection need not be at all similar to those that favor or prevent the spread of an infection, once it has taken place. This point is beautifully illustrated in an infection that tends to focalize like tuberculosis. In general, we can say that relative stasis is favorable to infection, but less likely to promote the spread of tubercle, while relative movement is likely to prevent localization of bacilli, but more prone to spread tubercle once the bacilli have focalized; that is, other factors like the numbers of bacilli and the character of the respective tubercles being equal. We find, therefore, that infection of the lung with tubercle bacilli is much more common at the apex where movement (of lung, of air current and of lymphatic flow) is relatively small, than lower down and towards the front where movements are comparatively great. It is the rule for first infections to occur toward the tops and

posterior surfaces where movements are relatively restricted by less yielding structures, as compared with the more expansile front and bottom of the thoracic cage. Similarly, pleural adhesions are in general much more abundant and of much greater extent above and in back than in front and below: and when they do occur in front and below they are likely to be attached to the ribs which are more fixed than the intercostal spaces.

Now, though first infection prefers the top and back of the lung, the tubercle that results therefrom is much more likely to reach quiescence and arrest than if infection takes place in the more movable parts of the lung. Even when tubercle formation has become extensive we become much more concerned about the formation of what we might call mid-pulmonary disease than about the same amount of apical disease. Clinical experience has taught us that in the former case we are dealing with a more serious condition than in the latter; and one of the reasons for this is that, as compared with relative inactivity, movement favors the mobilization and spread of focal products.

I have touched on this matter of the effects of movement and inactivity on two contrasting and different phases of tuberculosis, namely, infection and metastasis, because I want to protest against the confusion that usually involves any discussion of tuberculosis, when, as generally happens, it is assumed that what holds good in reference to the taking place of infection also holds as concerns its further development and spread, and when, as so often happens, the factors that govern therapy are mixed up or made identical with those that relate to prophylaxis. And I am further desirous of pointing out how inflammation can have two very different effects, depending on whether it is concerned with implantation of bacilli or an action on a focus already present.

As regards implantation, my argument has already laid it down that microorganisms that are brought to a tissue that is already inflamed fall on relatively resistant soil. But as regards the further development and spread of an already established focus, inflammation can exert an effect that may not be so favorable. Tubercle anywhere in the body is benign or innocuous just so long as its investing envelope is of such a nature that it is so impervious to the circulation of tissue juices that goes on between it and the host that the maximum amount of material absorbed is not enough to produce symptoms of intoxication in the host and the maximum of the kinetic energy of the circulation is not sufficient to mobilize bacilli and spread them. As sclerosis of tubercle proceeds, the interior of the formation becomes more and more shut off from the surrounding tissues. Now, anything that can bring about a better circulation around this avascular structure, anything that will promote an enhanced give and take between it and the surrounding tissue, will tend to "unlock" or "open up" this walled-in structure. Among other things this is exactly what inflammation—hyperemia, congestion, etc.—can do and frequently does do. And when it does this then inflammation becomes a contributory and inciting factor to the development of tuberculosis: not, remember, to infection with

tubercle, but to the spread of tubercle, or the development of tuberculosis. Here then we can look upon inflammation as we viewed movement—as capable of exerting two very different and antithetical effects, depending on whether we are considering either of two very different phases of what in the large is one problem.

Let us now come back to Major Webb's paper and the immediate questions that its subject matter raises. Major Webb finds that men with bronchi in a state of chronic inflammation do not develop the disease tuberculosis in larger proportions than men with what might be called more normal bronchi. The older view was that inflammations of the respiratory tract do, predispose to tuberculosis, and I believe that many assumed that this predisposition was a predisposition to infection. To-day, with our newer knowledge of the relative incidence of infection and morbidity, few of us, even without going into the matter further, would believe that, if men with inflamed throats and bronchi fell ill with tuberculosis, this disease was the result of recent infection. We should be more inclined to believe that the disease represented the awakening of old quiescent tubercle, planted perhaps years before. Therefore, on this basis alone, we should say that irritation of the upper respiratory tract in an adult played no part in infection. But we have in addition pointed out that inflammation, if it does anything, probably resists a fresh infection.

Now, if it were granted that inflammation does not lay a tissue more open to infection, but that on the contrary it probably plays a part in resisting bacterial invasion, it still remains for us to consider what effect constant irritation, brought about perhaps by some such stimulus as tobacco smoke, might have on foci of tubercle that exist in tissue. This set of circumstances would no doubt represent what more likely occurs under natural conditions: that is, some tubercle is already present in the lungs of individuals who take up the smoking and inhaling habit, and it is this tubercle that later blazes out into clinical disease, and again, therefore, it is this tubercle on which the inhaled cigarette smoke exerts an effect.

It will immediately occur to every one that if nearly everybody has quiescent tubercle and if inflammation can exert an awakening influence on such dormant tubercle and if frequently the ultimate result of the inhalation of cigarette smoke is a chronic bronchial inflammation, then why do not more cigarette inhalers develop tuberculosis? The answer is, that the factors are not so simple as this qualitative statement of the problem. To go a little further we must deal with the quantitative phases of the situation.

It is not to be doubted that while just enough and perhaps too much inflammation is bad for a tubercle, a little bit of inflammation either exerts no deleterious effect on it, or may, indeed, be good for it. We see this exquisitely exemplified in studying the influence of tuberculin on focal tubercle. All of you are aware that if sufficient tuberculin gets to a focus of tubercle it will cause the latter to react with inflammation. If now the focus is not too large, is not too much of the nature of a diffuse process and is well enough invested to begin with, and if the inflammation is not too intense, we may observe (at







*F. P. Mall*

BORN SEPTEMBER 28, 1862. DIED NOVEMBER 17, 1917.

least, experimentally) the most amazing results to follow the focal reaction, that is, inflammation. In a short time such a focus that may have persisted for weeks and months may disappear like snow before the summer sun, while non-reacted, non-inflamed foci in control animals go on to necrosis and dissemination. But too violent an inflammation in too acute a patch of tubercle can cause irreparable damage from the tissue death and spread of the process that it can bring about.

In the tobacco smoke inhaler we have a comparatively mild irritation, repeated often over a long period. What results is likely to be a chronic inflammation of a low grade. Everything else being equal, its net effects on tubercle that is otherwise being well taken care of should be mildly "stimulating" and tending to repair; not violently upsetting, as might occur from a lobar pneumonia in the area surrounding the tubercle. We should expect, therefore, that a number of divergent and perhaps opposing factors would balance one another, and that, as

compared with one thousand non-smokers, a thousand smokers would reach equilibrium.

What I have said applies only to the local irritating effect of tobacco smoke. This effect is to be kept altogether dissociated from any discussion of the constitutional effects of tobacco. Constitutional effects, such as the influence of tobacco on digestion, on the nervous system, on the vascular system, on the psyche, undoubtedly come into play and would have to be reckoned with in any broader discussion of the influence of the use of tobacco on the development of tuberculosis in general.

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## MEMORIAL SERVICES IN HONOR OF FRANKLIN PAINE MALL, PROFESSOR OF ANATOMY, JOHNS HOPKINS UNIVERSITY, 1893 TO 1917

A memorial meeting in honor of Dr. Mall was held on Sunday, February 3, 1918, at 4 p. m., in the hall of the Civil Engineering Building at Homewood. Addresses were made by President Frank Johnson Goodnow, of the University; President Robert S. Woodward, of the Carnegie Institution; Dr. William H. Welch, director of the School of Hygiene and Public Health of the University; Dr. Lewellys Franklin Barker, professor of Clinical Medicine in the University; Dr. Simon Flexner, director of the Rockefeller Institute and Dr. Florence Rena Sabin, professor of Histology in the University.

**President Frank Johnson Goodnow.**—We are assembled here to-day to honor the memory of our lamented colleague and friend, Dr. Mall. Dr. Mall had been up to the time of his death continuously and uninterruptedly associated with the medical school from the time of its opening. He was one of the group who a quarter of a century ago inaugurated a new venture in medical instruction in this country. The purposes which were then outlined, the ideas which were then entertained, the methods which were then adopted had subsequently a widespread influence throughout the land. It is somewhat difficult for us, separated as we are by so long a period from the original time of their formulation and accustomed as we are to the changes which they caused, to appreciate how novel and how important was the work then undertaken.

For the success attendant upon the medical school, Dr. Mall was in no small measure responsible. A brilliant and tireless investigator, he made invaluable contributions to the science to which he devoted himself and won prestige for the institution with which he was connected. A wise and sane counselor, he exercised a potent and salutary influence over the policy of the medical faculty. A kindly and courteous gentleman, he greatly endeared himself to his colleagues and associates.

Passing away in the prime of life and at the height of his powers he leaves in the world of science a gap which it will be difficult to fill, and among his friends a sense of loss which it is impossible to overcome.

We have, however, the satisfaction of knowing that the university, of which he was a member, is better and finer for what he was and did. His life and work will long continue to be an inspiration to the colleagues he has left behind and to the students whom he taught.

**President R. S. Woodward, Carnegie Institution, Washington, D. C.**—My acquaintance with Professor Franklin Paine Mall began about 20 years ago. We had met casually at that national center of biological interest, Woods Hole, and elsewhere, at frequent intervals during the decade and a half which preceded the more intimate association which began in 1912 and continued with increasing intimacy and attraction until the time of his death. During the year 1912, and especially near the end thereof, a number of conferences were held with him looking to the establishment on a permanent basis, under the auspices of the Carnegie Institution of Washington, of the researches in embryology to which he had long given attention. The conferences referred to and the more intimate relations which followed in the succeeding years brought about a degree of contact and sympathy which enabled us to understand one another to a degree rarely attainable. This experience has been especially interesting and instructive to me, and there appear to be the best of reasons to assume that it was similarly interesting and instructive to him. From its inception Professor Mall applied his unusual capacity for interpretation of the minds of men to me, and he appeared to be equally conscious of the fact that I endeavored also to make a special study of him and his char-

acteristics. I am not aware that he made any record of his observations upon me; there was no occasion for him to do so; but the untimely termination of his terrestrial career and the present memorial occasion seem to render it permissible to make acknowledgment of, and to record here, the impressions he produced upon me.

Since my association with Professor Mall had much to do with purely business affairs, in the development of his department of research, it is not improper to speak of his business abilities, although the world at large would probably not credit him with the possession of noteworthy capacity for fiscal affairs. There is, indeed, still, even in the twentieth century, a widely spread belief that men who are devoted to the pursuit of science, or to activities whose results are not measured in dollars and cents, are conspicuously lacking in business capacity. But this is a fallacy which will disappear under a closer study of the fundamentals essential in the effective conduct of affairs. It is commonly held, particularly in government circles, that those only possess executive ability who are trying to exercise it. Thus it is possible for one who has few qualifications essential to effective conduct of affairs to derive credit for remarkable capacity in such work, especially if he be able to depend upon subordinates to prevent him from going wrong. On the other hand, it is often said that executive ability consists in doing well what ought not to be done. But it would be wiser to say that executive ability consists in doing well and without ostentation anything that is worth doing. In this better sense of the phrase Professor Mall excelled. He possessed uncommonly clear vision. He held adequately considered theories of procedure, and he entertained a rational perspective of the relative importance of the factors involved in any case. He possessed all the elements, therefore, of superior capacity for the ordinary affairs of life, although he was never called upon to concentrate his attention exclusively on them.

His life was given rather to research, and his theory and practice therein are deservedly worthy of special attention. He held very distinct views on this subject. He understood very clearly that progress, resulting from research, does not consist simply in innovation, much less in eccentricity. He understood, likewise, that progress does not consist in the mere accumulation of facts in accordance with well-known methods. He had no fear of breaking with precedent. His criticisms were sometimes mistaken for iconoclasm; but while they were often destructive, they were also, in general, highly constructive. He was exceedingly fertile in suggesting better ways of doing things even in matters which lay outside his special interests. Whatever entered his mind was visualized in a variety of aspects. He was surprisingly quick in separating the essentials from the unessentials of any question presented to him.

Of his work in science, I am not qualified to speak except in general terms. He was a specialist in certain branches of biology, and in these he developed processes peculiarly his own. But in their general aspects his methods are the well known

methods of science, and one does not need to know much of his technique to discover the reasons for his remarkable capacity for productive work. His sincerity, his industry, and his comprehensive knowledge of his work carried with them conviction and confidence. He entertained always a clearly definite plan for any piece of work, having set items in his program for every step from the initial observations, investigations or data, to the final publication of the results and the distribution of them to experts who might be expected to appreciate and hence to make effective use of them. He understood uncommonly well the value of system; but he never permitted the mere machinery of research to absorb his attention or to deflect him from his principal objects. He made extensive use, for example, of card catalogues and bibliographies but always as means to rather than as ends in his investigations.

Professor Mall possessed certain notable characteristics which were manifested in striking fashion often in conferences with him concerning subjects of special mutual interest. He was a man of few words, he was never prolix in argument, and he knew well when a conference was finished. He was able always to concentrate attention on the salient features of a subject under discussion. He was extremely reasonable with respect to matters of controversy and this made it a source of pleasure to confer with him even when differences not easily dissipated arose; for his manifest desire to have the adjustment of every question depend on its merits was always an assurance that the right conclusion would be ultimately reached.

Summarily characterized, Professor Mall was an ideally typical man of science. He tried to visualize the universe as it is; or, in more common parlance, he looked at, and sought always to see, things as they are. His perception of reality and his conformity to it were noteworthy in all his activities. He was able to see much more clearly than most of us that limitations exist on every hand. Men of science, generally, and mathematicians even, are not infrequently found to entertain an inadequate respect for the rules of elementary arithmetic; but this is a defect of the human race rather than of any class of men, as is well demonstrated by the fact that professional financiers show least respect for those rules. But in an age when many good men have lost their heads, temporarily, at least, in respect to the possibilities of the ways and means available for promoting research and discovery, the equilibrium of Professor Mall remained undisturbed. His foresight was singularly free from the fogs and the illusions which often diminish the efficiency of enthusiastic investigators. He knew well how to count the immediate costs as well as to estimate the ultimate consequences of the researches to which he was devoted.

Quite naturally and gracefully the mental qualities already alluded to were supplemented by correspondingly high moral qualities. The two kinds of qualities were, indeed, inseparable in him. They were neither stored in separate compartments nor restricted in use to separate days or occasions; the entire man was always visible and available in his presence. Where he stood, or what he thought with respect to any question to



which he gave attention was never a matter of doubt. He faced his colleagues with the same frankness and the same truthfulness with which he approached the problems presented by his favorite science. It is in this rare combination of mental and moral traits that we find the foundations at once for his signal success as an investigator and for the affectionate and abiding regard he won from all those who had the good fortune to share in his more intimate friendships.

**Dr. William H. Welch** (Abstract).<sup>1</sup>—Dr. Welch outlined briefly Dr. Mall's medical training and the steps which led him to the laboratories of His and Ludwig in Leipzig, where he and Dr. Welch first met in the winter of 1884-85. Speaking of the great influence which these two men had upon his scientific development, Dr. Welch said:

Ludwig's was, I believe, the stronger and more personal one; that of His was more in methods and the specialized problems of embryology. I had worked in Ludwig's laboratory 10 years before and he often spoke to me rather freely. I doubt if he ever had a student to whom he was more attached, or who had made a more profound impression upon him than Mall. He more than once spoke to me of Mall's remarkable intellectual qualities.

At that time Dr. Welch had already been called to The Johns Hopkins University, and upon his return to America he received a letter from Dr. Mall expressing a desire to come here and work. In consequence he came to Baltimore in 1886 as fellow in pathology.

While in the pathological laboratory he was, as you may imagine, an independent worker; it was a delight to have him there. He assisted in the course in bacteriology, and his methods then had the same originality that has always characterized them. He was interested in connective tissue and discovered that certain varieties of bacteria had the power of digesting certain kinds of connective tissue.

At the end of three years he went with Professor Stanley Hall to Clark University, and later to the University of Chicago. He had made the acquaintance of President Harper while in Leipzig, and the two were close personal friends. It was with some misgivings, therefore, that Dr. Welch, at the request of The Johns Hopkins University, set about to induce Dr. Mall to return to Baltimore at the opening of the medical school in 1893. The plan of the school, however, appealed strongly to Dr. Mall, and although every effort was made to keep him at the University of Chicago, he accepted the new post. Of his work here Dr. Welch said:

Mall belonged to the group made up of those men who came in the early days of the hospital, in 1889, and those who came as workers in the scientific laboratories of the new medical school in 1893. He is the first of that group to be taken away. I think my colleagues will agree that, of all that early group, he was the most productive contributor to science and one of the most stimulating influences. There is no expressing the loss which this school and university, and we, his colleagues, have suffered. He was wise and sound, and had a great insight into the value of things. I know of no one whose powers of mind were more pene-

trating. He, more than any of us, perhaps, represented two of our educational ideals—freedom in teaching, freedom in learning, freedom of the teacher, freedom of the student. Indeed I may say that President Gilman, having once selected a man whom he considered qualified as the head of a department, left him a pretty free hand. Mall entered into that spirit most thoroughly, and was undoubtedly a very inspiring influence for the better students. That was one of the ideals he stood for. The other was, that the primary qualification of a preceptor should be the capacity to produce or to stimulate production. These two ideals he never lost sight of, and in him they were exemplified to a surprising degree.

He was to all of us a delightful companion, and it was a joy to be with him. He was attractive and had a whimsical way of saying things, but he was very wise. He ranks with Rowland as one of those men who have added lustre to the university by their contributions to science, and who, by their revolutionary influence upon their subjects and their great capacities as teachers, have led others to become teachers. One has only to consider what anatomy stands for in our medical schools to-day, as compared to what it was when Mall began his work, to appreciate what his influence has been upon the science of medicine. His memory is, indeed, one of the most precious possessions, not only for us, his colleagues, friends and admirers, but for all times of this university.

**Dr. Lewellys Franklin Barker.**—Adequately to present the personality of Franklin Paine Mall, to describe the essential qualities of his character, and to do justice to the distinctive excellences of his intellect, would require the pen of an expert psychographer, the selective ability and the power of artistic composition possessed only by a skillful naturalist of souls. It is to be hoped that, sometime, an experienced practitioner of the art may supply us with the fair and right account that we should like. Those of us—pupils, colleagues, and friends—that are gathered to-day at this memorial meeting can scarcely do more than contribute materials and clues that may later on be an aid to the definitive production that will be proportionate and satisfying.

No one who enjoyed close association with Mall during his 25 years professorship at The Johns Hopkins Medical School could fail to recognize a unique personality, whose significance for medical science and especially for anatomy in this country was outstanding; and those who were admitted to the circle of his friends counted the experience as one of the most rewarding and precious of the privileges of their lives. For some five years it was my good fortune to be his assistant in the anatomical laboratory here, and, seeing him daily in his work, I had manifold opportunity to become impressed with his powers and his activities as investigator, as teacher, and as educational reformer; and, above all, I came to know him as a man and a friend. Concerning his work as an anatomist Professor Sabin is to speak; I shall refer to his anatomical work only in as far as it throws light on the intellect and character of the man.

Mall's greatest professional interest lay in the promotion of original research in anatomy and especially in human embryology. His appetite was whetted for the pleasures of the intellect. He enjoyed accumulating facts but he longed still more for that most exalted of intellectual pleasures—the discovery of truth. He had an inexhaustible enthusiasm for the

<sup>1</sup> Owing to the continued absence of Dr. Welch in connection with his work in the office of the surgeon-general of the army, it has not been possible to give his address in full.

study of form and particularly for inquiries into the genesis of form. He delighted in finding (and fixing in enlarged reproductions that are permanent records) the several stages through which the body, or a part of the body, passes from its first formation in the embryo onward toward complete development. In his opinion, not much progress in human anatomy can now be expected from mere dissections of the adult human body; advances in our knowledge of human structure can come only by way of microscopic and chemical studies of the parts or by investigations into the genesis of the organs and tissues of man and animals. An institute that attempts fairly to represent the subject of anatomy must, of course, be prepared to teach and to study the mature body of the highest animal form, but it must also, he thought, concern itself largely with the origin and development of the individual being (ontogeny) and with the racial evolution of the type (phylogeny). Though his own interests lay more in embryological than in comparative anatomical inquiry, he had a deep sympathy with both modes of attack and was ever ready to encourage researches in either direction. His attention was early drawn to pathological human embryos and throughout his life he collected these as well as normal forms and subjected them to intensive study by the newer methods. Though predominantly a student of form, he was by no means insensible to the delights and the rewards of the study of functions; indeed a number of his researches were directed toward the solution of what might be designated physiological-anatomical problems, such as the determination of the functional-structural units in the liver and of the vascular supply of the several viscera. The influence of the teachers that inspired him—Welch in pathology, Ludwig in physiology and histology, and His in embryology and histogenesis—was evident in the directions that his work took, but his period of tutelage was brief, his problems were his own, and he will always be distinguished as one of the independent thinkers and investigators of our time.

His method of teaching was unusual. He rarely, if ever, lectured. Not that he thought the lecture of no didactic value; on the contrary, he was a firm believer in its stimulating effect when properly prepared, illustrated and delivered. But he felt that he himself could teach better in other ways, and he relegated the lectures to other members of his department. He was, however, a master of what is called "elbow-teaching," and no student who has ever been at his elbow will ever forget the character of this relationship—his trenchant comments, his startlings of the intellect and emotions, his humorous and sometimes satirical thrusts, and, above all, his earnest and sincere desire to make the neophyte an independent worker. New students often failed to understand him. Accustomed in the college of liberal arts to lucid exposition, to measured tasks of memory, to recitations on text-book reading, and to the performance of laboratory work so carefully planned and described as to leave but little room for personal initiative or for independent thought, many of the freshmen in the medical school felt "lost" when they were told by the professor in his white gown to begin the dissection of a part, using atlas

and text-book as guides, without any special instruction as to where or how to begin, without description of what was to be observed, and with no intimations that definite amounts of work should be performed in given spaces of time. Of course, they floundered, and often they bitterly complained. The method was drastic, and some, I fear, never understood its purpose. For most students with good natural endowment, however, the compulsion to realization of the fact that on entrance to the medical school the period of spoonfed education was over and that the time for acquiring the power to work more independently had arrived, though abrupt and perhaps painful, was most salutary, and I have heard many a student admit that he owed to Mall's method his intellectual awakening and his first arousal of desire to become an independent scientific worker. Mall's contempt for slovenly or dishonest work, his admiration of a rigidly perfected technique, his encouragement of objectivity in study, his insistence upon familiarity with the bibliographic sources, his emphasis upon the duty and pleasure of extending, rather than upon merely acquiring, knowledge, his impatience with inaccuracy and with stupidity, his unswerving loyalty to the highest ideals of natural science—all were qualities that made him a working companion of inestimable value to the young men and women who entered The Johns Hopkins Medical School. His influence upon the rank and file of the students, large and beneficial as it was, was even exceeded, however, by the effect he had upon the small group of more original minds in each class and upon the members of his staff. Mall had a nose for the potential scientific investigator. With almost unerring accuracy he would scent out young talent and give it special encouragement and opportunities. Not all buds, it is true, opened in that atmosphere—a number have found conditions more favorable to the unfolding of their special talents in other departments later in the course—but it is interesting in looking over the scientific publications of graduates of our medical school to note how many of their authors began to evince an interest in original inquiry while in the anatomical laboratory. It was largely owing to Mall's early capture of promising young minds that so many have found a career in anatomy interesting and satisfying, and that a large number of the chairs of anatomy in American medical schools are now filled by his pupils. A still larger number who were led by him to undertake original inquiry have continued to be scientifically productive in other fields of medical science, pre-clinical and clinical. It was a principle with Mall that any department in a university should teach its subject for its own sake, without too much concern for its application to the work of branches to be pursued later in the student's course. He maintained that it was not the business of the department of anatomy to teach the so-called surgical and medical applied anatomy, for these subjects properly belong, he asserted, to the departments of surgery and medicine. From this position he could not be budged, either by the imprecations of clinicians or the threats of State Board Examiners. By his own special methods of teaching, however, and with the aid of a carefully selected and well-organized teaching staff, he fulfilled the

function of a university teacher, for he saw to it, first, that undergraduates secured a knowledge of the main facts and principles of his science and some acquaintance with its practical-technical methods of investigation; and, secondly, that numerous workers were induced to pursue anatomy as a career, devoting the rest of their lives and energies to the teaching of the subject and to original inquiry in some one of its divisions.

Though the character and intellect of the man are well revealed by his activities as investigator and as teacher, it would be remiss not to speak of his ability as organizer, and of his wisdom as counsellor and educational reformer. Mall appreciated more perhaps than most directors of scientific institutes the importance of the best material equipment for his laboratories, and made rigid rules to provide for its care and to prevent its deterioration. He trained technical assistants to relieve the scientific staff of much routine work. He believed that every laboratory director should be a good house-keeper, and the scrupulous cleanliness and perfect order of his institute, marvelled at by all who had grown up under an older anatomical regime, reflected his opinion that the character of the surroundings in which people work exerts a moral effect upon their conduct. Mall's organization of the Anatomical Laboratory of the medical school and later of the Embryological Institute of the Carnegie Institution was based upon a differentiation of function and a corresponding division of labor among the members of a staff. He knew how to delegate large responsibilities to subordinates, how to correlate the several activities of his department and how to maintain the oversight that is necessary to ensure the satisfactory progress of work. Indeed, he made his own the three watch-words of every successful executive, "Organize, Depute, Supervise."

As a counsellor, Mall's advice was sought not only by those interested in anatomy but, and especially, by the leaders in this country of reforms in medical education. University presidents, heads of science departments, members of the directing boards of scientific institutes, and professional investigators of the evils of existing educational systems, conferred with him and were profoundly influenced by his opinion. In a number of articles that have been published since 1890 upon the improvement of the conditions in our medical schools and hospitals, the "insider" will have no difficulty in recognizing the tricklings from a well-known stream. He favored the foundation of whole-time clinical chairs in our medical schools and the writers who first urged this reform owed their seed-thoughts to stimulating discussions with him. In faculty meetings, and in large groups generally, Mall was retiring and for the most part silent. He was at his best tête-à-tête, for under four eyes, or in small groups, his taciturnity disappeared, and his speech to the sympathetic listener was free and always inspiring. His conversation was peculiarly stimulating to his friends on account of a certain cryptic character that depended on the frequent elision of associative links. His own mind worked so rapidly that it appeared to make leaps rather than to flow, and the interlocutor who was not agile enough to leap

with him, or to intercalate for himself the materials necessary for continuity, would sometimes be at a loss to understand him. More than one man has been heard to say that he "could not make head nor tail of what Mall was saying." But to him who could and would follow, how rich was the reward! Mall's example as an organizer, his wisdom as a counsellor, and his zeal as an educational reformer, have given the progressive movement in American science an impetus that will continue long after his death.

A man absorbed in scientific pursuits does not always take time for the enjoyment of home and friends, or for the satisfaction of the æsthetic desires. But Mall was singularly happy in his home life and no one ever had stauncher friends or was more loyal in friendship than he. Married in 1895, he found in his wife one who could sympathize fully with his work, who could share his ideals, who, with him, could disdain mere externals, and who felt it no sacrifice to give up many material and social pleasures when they conflicted with the interests of the higher intellectual life. To their home, personal friends were always welcome, and on Sundays and holidays members of the laboratory staff were frequently entertained there. Mall's personal solicitude for the welfare of members of his staff was touching. His suffering was acute when they were in trouble, and when successes came to them he was elated. He had no desire for, or satisfaction in, promiscuity of social relationships, but wherever he was—at Clark University, at the University of Chicago, or in Baltimore—he drew to himself a small but congenial group of intimates, and to them he gave himself freely. Those thus advantaged were impressed with the fusion of sound sense with earnest enthusiasm that was characteristic of him. A little tinged with pessimism, he was, in reality, a meliorist, knowing that there is much to do (that can be done) to better man's estate. He had strong faith in the beneficent power of truth and of work. He believed in freedom of thought and he practiced freedom of speech. He was a striking example of a strong and a liberal spirit. Memory of him will continue to move the souls and to keep warm the hearts of those who knew and loved him.

**Dr. Simon Flexner.**—The death of Doctor Mall is so recent and my grief for his loss so fresh that I find myself reflecting on the fruitful and delightful memories of our past association instead of writing out my impressions of his unusual personality.

Doctor Mall returned to Johns Hopkins in the late summer of 1893, just before the medical school opened its doors to the first class of students in the autumn. It was then that we met. I recall vividly my excitement and nervousness when the rumor was circulated about the old pathological building that Mall had arrived. His name had been a tradition among the small group in the pathological department. A few years earlier, before the hospital had been opened to patients, he had come to the laboratory and, as fellow in pathology, had performed a miracle of interesting and important studies on the connective tissue foundations of the organs. Fellows in



pathology there had been since his time, but no one whose memory was glorified as Mall's had been. We had so often heard him and his work spoken of by Doctor Welch, Doctor Halsted, and others, including the indispensable Schultz, who was for many years presiding genius over the technical and janitorial services of the laboratories and whose commendation carried with us such great weight, that I pictured Mall as quite different from what in actual life he proved to be.

One's fancy—my fancy surely was so—when young is apt to produce its own pictures. In my fanciful portrait of Mall I represented him as large, absorbed, and rather austere. Never was a fancy more completely and happily shattered. I can just remember our meeting; those who knew Mall well will never forget how engagingly he smiled. It was with one of the best of his smiles that he greeted me.

That event was the auspicious beginning of a warm friendship which never wavered until his death. During the first period of half a dozen years we were in almost daily contact. Later, and after 1900, when I left the medical school to enter the University of Pennsylvania, our meetings were at first not infrequent. I shall never cease to regret the increasing intervals between them which followed my removal to the Rockefeller Institute in New York. Increasing responsibilities and broadening duties play sad havoc with one's life, and I feel that I suffered a grievous and now irremediable loss in permitting those circumstances to cut me off to the extent it seemed inevitable they should from association with Mall. To a certain extent, letters took the place of personal contact. Thus I kept more or less in touch with the workings of his restless and constructive mind.

It probably will strike few except his very intimate friends that Mall was by temperament a reformer. He was an uncompromising democrat and hence entertained the firmest belief in liberty in its true and proper sense. Out of this intensity of conviction arose the views expressed in conversation more frequently but not more forcibly than in his addresses, on full opportunity and freedom in university education, both in its pregraduate and postgraduate aspects. His comprehending and incisive mind was the first, I believe, to appreciate and afterwards to propound that the best of medical educational institutions were half-hearted affairs. The part of the institution which a quarter of a century earlier had been the weakest—the laboratory branches namely—had been immeasurably strengthened in that short period, during which the previously stronger part—namely the clinical branches—had progressed relatively little. The balance could be struck and must be, even though in the process the old system were, if need be, completely shattered, as much shattered indeed as had been the earlier hybrid combined laboratory and clinical chairs. Out of this conception which Mall propounded, I am almost inclined to say preached to us persistently, arose the present movement ever gaining force and strength until it has now become almost irresistible, in favor of full time clinical professorships.

It is very interesting to consider just here the extent to which he used others, converts or disciples as they may be

called, to diffuse more broadly his reforming ideas. One would search Mall's miscellaneous papers, of which, indeed, there are notably few, in vain for an exhaustive presentation of the case for the full time clinical plan. The wide dissemination of the idea by the printed page was left to others, while he maintained the high level of conviction in those coming under his immediate influence by an irresistible fund of logical exposition.

In his delightful essay on his master, Wilhelm His, Mall reveals his attitude toward higher education in its various complex aspects. I wonder how many returned foreign students have kept up an intimate correspondence with a revered teacher extending over a long period of time, like that disclosed by Mall in this essay. The extracts from his letters there published show how well the older man comprehended the younger, as the spirit and substance of the essay show how the younger man admired and appreciated the older. There is no doubt that His perceived in Mall rare personal and mental qualities, as he confides to him not only the subjects and trend of work, but his larger aspiration in the wide domain of anatomical research. In the light of the relation there revealed one can surmise the satisfaction and joy with which His, had he lived, would have welcomed the establishment of the Institute of Embryology with Mall as the first director.

In my task of presenting a fragment of the personality of Mall as apparent to his intimate friends and associates, I find myself embarrassed by the many memories that crowd my mind. It is not easy to select episodes. I love, myself, to think of the period during which he lived, as did the medical officers, in The Johns Hopkins Hospital, for then we were almost constantly together. The small, older group of men—older, that is, than the internes—saw much of one another. Mall, Frank Smith, Thayer, Barker, and I met always at dinner, frequently at breakfast and luncheon at the small table at the head of the room. There was lively conversation and much variety of theme; and not a little good cheer. A small photographic print still exists which pictures the group; it is chiefly notable for the good likeness of Mall which it presents, showing him as it does in one of his happiest moods.

Mall returned to Baltimore as the first professor of anatomy of the new medical school. The physical conditions surrounding the launching of the medical school were so simple as to be almost austere. Aside from the hospital—a model of completeness at the time—the plan for housing the new departments of the school we should now regard as meager in the extreme. I sometimes think that it may be well to recall from time to time the simple beginnings out of which the great institution of The Johns Hopkins Medical School arose. The only additions made to the hospital buildings, to accommodate the departments of anatomy and physiological chemistry and pharmacology, were two stories added to the original small pathological building erected as a mortuary for the hospital and already housing the entire pathological department. It was in the upper, or fourth story of that enlarged building that the complex department of anatomy took origin.

Some one else, who traces the growth of anatomy at the medical school, can tell better than I can how Mall adapted the limited space and facilities at his command to the teaching of anatomy, histology, and embryology, and to the conduct of research. There was no actual break in the continuity of his own investigations, and very soon after the medical classes were taken in he began to produce the new work which in a steady and increasing stream has come out of the anatomical department.

There were not a few obstacles to be overcome in getting the student's work properly started. I recall the shifts he was obliged to make to bridge over the gaps in dissecting until human cadavers became available. This period was for Mall, in many ways, an anxious one. But it was not long before this particular obstacle was overcome, and because of the improvements which he introduced in the preservation of human cadavers, his laboratory soon became the custodian of all the anatomical material employed for dissection and surgical instruction throughout the city.

The kind of teaching which Mall gave to his students has been described; there was no lecturing in his curriculum. He had almost a horror of lectures in anatomy; the idea collided with his fundamental conception of how so practical a subject is to be acquired. In his views there was one road only to that goal. The student must teach himself in order to learn. Hence there were provided the objects to be dissected, text-books, atlases, models, and time, with a sufficiency but no excess of instructors or guides. He saw no virtue in exhibiting and describing a pre-dissected part, provided the students were given opportunity to dissect for themselves. That this principle is sound no one will, I think, now deny. That its operation has produced a remarkably large number of superior, independent, and broad anatomists, the history of his department amply shows.

But a confusion of method and man is often made with disastrous consequences. It is easy to imagine this mode of teaching anatomy adopted widely without yielding the results which Mall obtained. To put the method into effect would doubtless represent a great advance over the old system, but without a strong, able teacher and guide, such as Mall was, the phenomenal results which he achieved would not be attained. In other words, he was a sound innovator because he was a strong man. He was a successful leader in anatomy because he was learned and original. He has left a rich heritage to science through his own labors and those of his pupils, because to all his other qualities he added the rare ones of wisdom, kindness, and generosity.

Our proximity in the pathological building brought us into frequent association. In the early days of the medical school, Mall often attended the autopsies, many of which I performed. His active interest in the pathological phenomena continued throughout his life, in part possibly as the result of the year spent as fellow in pathology under Doctor Welch. But in fact he did not dissociate, as is often erroneously done, facts of pathology from those of anatomy. Being naturally inquisitive in regard to the relation of cause and effect in respect to

the unit forms of organs, he was also prone to inquire into the effects of causes in their nature pathological.

At about the period when Mall was studying the lobular unit of the liver I was induced to attempt the application of some of the methods he worked out to cirrhosis of that organ—a mere illustration of the way in which two related departments through him were made to react on each other.

I imagine that few who knew Mall even quite well realize with what intensity of absorption and application he would work at a problem once he had gripped it, as one might say. In temperament he was naturally reflective. Hence there occurred periods during which he appeared to be doing little in his laboratory. At such times he would become possessed with the impulse to roam about the building or out into the city or into the adjacent country. It was remarkable that when under the influence of those moods he did not seek solitude so much as another form of activity. I was not infrequently taken away by him for a stroll through East Baltimore, and on these expeditions I acquired quite a knowledge of that part of the city. They were in many ways extremely interesting occasions, for during them he often talked his best and sketched advanced ideas on educational and other reforms, as well as on problems of research. I think Mall never dreamt idly. He was possessed of a romantic imagination, but it was both controlled and constructive. To not a few who did not understand him well his ideas sometimes sounded extreme, but they invariably rested on real foundations, as is now evident since so many of them have been carried into practical affairs.

At other times he worked out problems in his laboratory with consuming intensity. It would seem as if while under what I have called the spell of his reflective mood, a problem would formulate itself more definitely, or some barring obstacle give way to a revealed point of view. However that may be, my notion was that the periods of reflection were signs that he would attack a new or solve an old problem; and I always looked for new ideas and accomplishments when the mood changed.

If I have at all succeeded in revealing Doctor Mall as he appeared to me, then I have presented to you a complex personality. The remarkable thing is the way in which all the pronounced qualities that characterized him were fused into a simple, harmonious, kind and lovable individuality. I have referred already to Mall's democratic spirit. He was an intense lover and active exponent of liberty. His belief and confidence in freedom extended far beyond the confines of the university and laboratory, and into the world of politics and government. Freedom within the university he held as the first condition of the successful struggle of the forces of light over superstition and darkness. Within the walls of his laboratory the fullest liberty prevailed. Once outside the realm of the prescribed task for training, each man followed the bent of his own talents and tastes. However, his principles as well as his practice sharply differentiated between liberty and license; hence the rise under him of a group of strong, independent, but sound teachers and investigators. Mall would probably have combated the suggestion that he produced a

school of anatomists, using the term in its usual significance. He would probably have insisted that he merely continued in America the system which he pursued or saw in force in Switzerland and Germany. But I believe rather that he made such definite contributions to the higher education and training of anatomists, and produced in, alas! a few brief years so large a number of varied and capable teachers and investigators, as to mark a new era in the history of higher educational endeavor.

I said that his deep convictions on freedom carried him into the wider domain of social liberty. Mall never propagandized on this subject. Nevertheless, he felt intensely about it. It is noteworthy that with all the admiration for the freedom of migration from university to university and the wide election of subjects and ideas in the German university, to the social and political conditions of that country he was antipathetic. To so strong a "democrat," to use that term in its wider and better significance, a studied paternalism and imperialistic tendency were deeply unsympathetic.

Mall's sincerity, self-effacement, and never failing consideration were at the root of his noble qualities and made companionship with him a rare privilege. I have already spoken of my own good fortune in possessing in some degree his intimate friendship. It is a rare possession, indeed, and one to be cherished. But I owe him also an educational impress, none the less valuable because of its subtle nature. I am of the opinion that his pupils were influenced by this unusual quality which because of its elusiveness seems an emanation—so little was it given off or received with immediate conscious perception.

Mall was absorbed in ideas. They formed the substance of his serious talk, but he was by no means a stranger to the lighter side of human relations, for he possessed a gentle and engaging humor which might even, when provoked, become a little biting. It took time and skill to penetrate an outer film of reserve which arose from innate modesty and shyness, but once beneath that protective covering, one readily discovered in him a simple, idealistic, and gifted person of many sides, possessed of an almost miraculous power to stimulate students to put forth their best efforts. His memory and example will long survive in the achievements of his students and associates, in the broad ideas which he disseminated, and in the admiration and affection which he inspired.

**Dr. Florence Rena Sabin.**—To those who are familiar with the history of medicine in this country it is a matter of common knowledge that at the time Dr. Mall began his career, 30 years ago, anatomy in America had no scientific standing, a mere tool of surgery, with but a single method, that of dissection. He left it where it must be, and always has been in any community where medicine is progressive—one of its great sciences. He has left it richly endowed with technical methods, a science so truly fundamental that the workers in every other branch of medicine are constantly and increasingly returning to it, both for methods and results. The vision of this change must have been his while he was yet a student for he wrote in one of his letters: "My aim is to make scientific

medicine a life work. If opportunities present I will. This has been my plan ever since I left America and not until of late (since having received encouragement) have I expressed myself. I shall no doubt meet many stumbling blocks, but they are anticipated."

Sweeping aside the traditions of the dissecting room, he first created conditions under which this change could develop, and then devoted himself to scientific achievement, and to the type of teaching in which he was profoundly interested. It was one of his oft repeated maxims, that the best, and perhaps the only great way to teach, is by example. With the ideal of scientific work as his goal he has left us an example so rich in ideas, so varied in technical methods and so representative of the range of anatomy and embryology, that a study of his work is both an inspiration and an education.

His very first undertaking in the field of research serves well to illustrate his independence of thought which to those who knew him was one of his most striking characteristics. During the winter of 1885 he began his scientific work under His at Leipzig, who gave to him the study of the gill-arches in the chick. Four years prior to that time His had studied the same region in a human embryo. He noted that the gill-arches do not break through into the pharynx, but that a depression of the ectoderm develops over the region of the third and fourth arches, and concluded that the thymus must arise from the ectoderm of this depression. Dr. Mall evidently made his study independently, cut his own series, made reconstructions and came to the conclusion, now generally accepted, that the thymus arises, not from ectoderm, but from the endoderm lining the pharynx. At the end of the winter's work he presented his results to His in the form of a finished manuscript in English. His could not, however, accept this conclusion so directly opposed to his own view and asked his pupil to restudy the subject. This he did the following winter while in Ludwig's laboratory, translating his manuscript into German. The work was given to His a second time and accepted for publication, just as Dr. Mall was leaving for Baltimore. In the next number of the journal of which His was editor, there appeared a second communication from the latter, strengthening his own point of view, but announcing that a different opinion would be published by one of his pupils in the next number. When Dr. Mall's article appeared it was with a damaging footnote by His, to the effect that the independent character of the results was obvious. During his early months in Baltimore, Dr. Mall established his point in a mammalian embryo, and two years later His restudied the region in a human embryo and found that Dr. Mall's conclusions were correct. He gave due acknowledgment in an open letter to Dr. Mall published in the same journal in which he states frankly, "Sie haben gegen mich Recht." This letter cemented a life-long friendship, as can readily be seen from the correspondence accompanying Dr. Mall's article, "An estimate of the work of His."

<sup>1</sup> His, W.: Schlundspalten und Thymusanlage. Aus einem Briefe von W. His an F. Mall in Baltimore. Arch. f. Anat. u. Phys., Anat. Abth., 1889.



During the winter of 1885, His suggested that Dr. Mall work under the great physiologist, Ludwig. As Ludwig's laboratory was always full, the opportunity was slow in coming; indeed, as Dr. Mall wrote home, he was leaving Leipzig with no hope; his trunk was even on the way to the station when the letter came that the opportunity he so much desired was his. So great was the influence of Ludwig over his mind, character and future work that it is impossible to overestimate it. He himself summed it up in these words, "To that master I owe much—all." Ludwig assigned him the study of the villus of the intestine. As he stated in one of his letters almost his first impression was that here was a subject which had occupied the minds of the greatest anatomists of the past century. Repeatedly throughout Dr. Mall's writings there is to be found that expression of regard for the work of great minds. Widely read in his own subject, it was of the works which have lived and will live that he made a profound study.

In Ludwig's laboratory Dr. Mall learned the methods of injecting blood-vessels and lymphatics, and his studies of the vascular system of the intestine and stomach are familiar to every student of medicine. Under the influence of Ludwig, his work was characterized by a very strong physiological bent. Indeed, it may be said that his work was physiology in the hands of one with an intense interest in structure. In the work on the intestine, and more clearly still in that on the stomach, he was absorbed in the mechanism of all the parts of the organ.

In some of the foreign universities it was the custom for a new incumbent of a chair to deliver an address giving, as it were, a "prophecy" or a "program" of his future work. Such a program was the famous address of His on accepting a chair in the Swiss University of Basel. In some such way the article of Mall on the stomach, published in the first volume of The Johns Hopkins Hospital Reports, gave his program of the way in which he proposed to study anatomy. This paper lays a foundation for what may be called *physiological anatomy* and in it can be traced the beginnings of many of Dr. Mall's ideas. He studied the stomach from every aspect and with a wide range of methods. There were experiments in digestion bringing evidence to support the view that the acid is secreted only in the region of the fundus; here is the beginning of his brilliant studies on connective tissue, in which he became interested through noting the arrangement of the fibers of the submucosa. Here also are observations on smooth muscle which led to the study of the types of contraction-waves in the intestine, and later to experiments on the reversal of these waves. In his paper on the stomach is this brief note: "Recently I have found that irritation of the splanchnic nerve causes contraction of the mesenteric vein." He probably first made this observation in Ludwig's laboratory, and subsequently proved that the portal vein is supplied with vaso-motor nerves, one of the valuable discoveries in physiology.

The most important idea of his early work from the standpoint of anatomy, was that of structural units, which Dr. Mall conceived from the study of the villus. He noted that the villus was the unit of function of the intestine, and this theory

of structural units can be followed through a long series of investigations, in part by himself and in part by his pupils. In fact almost every organ of the body has now been studied from this point of view, and almost every organ except the nervous system can be simplified by this conception. The theory reaches its best expression in Dr. Mall's own articles on the liver and spleen, in which he states that organs are made up of ultimate histological units represented in the vascular system by the capillary bed which intervenes between a terminal artery and its corresponding vein. At this point the two cease to accompany each other and are separated by the maximal distance, that is the length of the capillaries. Thus the length of the capillary determines the size of the unit. These ultimate histological units are grouped together into lobules which vary considerably in the different organs of the body. They are not only of great structural significance, since an organ is to be considered as a multiplication of them, but are also of significance to physiology, since such units are equal in function. For example, a unit of a gland gives a unit of secretion. This equality in size and function comes from the laws of growth of an organ; when a unit increases in size, so that the length of its capillaries increases beyond the norm, a new artery develops, the single unit splitting into two. Thus, from the general theory of structural units, Dr. Mall was led into one of the aspects of the problem of growth; namely, how a small organ becomes a large one. This problem he often discussed in the laboratory. In his article on the liver he gives the clearest expression of it. There he develops the theory of Teile and Sabourin that the portal unit, not the hepatic lobule, is the real unit of structure and function, since the portal units are equal in size and are also the centers of growth in the liver. During growth these units are constantly fractured and destroyed as new units develop, and it is this interstitial growth in organs which makes the subject so difficult to follow.

In his study on the spleen Dr. Mall brings out best the relation of all the tissues of an organ to its function. Thus the spleen is an organ based upon the vascular system; its histological units are grouped into lobules which are outlined by dense bands of connective tissue. The arteries in these lobules end in swellings—the ampullæ of Thoma—where the endothelium changes from the typical complete lining of a blood-vessel and becomes a reticulum with open meshes. This change in the endothelium, demonstrated histologically by Mollier in 1911, had been fully described by Dr. Mall 11 years earlier. Through these openings in the ampullæ both the blood-plasma and the corpuscles pass freely into the pulp and thence back into the rich plexus of veins which fill the lobule through corresponding holes in their walls. By experiments Dr. Mall showed that the emptying of the pulp-spaces into this plexus of sinusoidal veins is accomplished by means of the contraction of the bands of smooth muscle in the trabeculæ. As these bands contract, the trabeculæ of reticulum upon which they run tend to pull open the interlobular veins, while at the same time they compress the arteries. Thus the splenic pulp, one of the most difficult enigmas in histology, is seen to serve as the capillary bed of the spleen. This study of structural units

grew out of the work in Ludwig's laboratory, and may be considered as the foundation for a new phase of anatomy, a step beyond morphology, *i. e.*, the study of the adaptation of the minute structure of organs to their function.

More than any other anatomist, Dr. Mall has also enriched our knowledge of the fibers of the connective tissue. He analyzed the differences between elastic fibers, white fibers and a modification of the latter—the reticulum, which forms the framework of organs. In this study he used the methods of bacteriology and of chemistry, adapting them to his needs and producing the most beautiful specimens of reticulum to be found in anatomical literature. This study he illuminated by showing that the framework of organs is not an inert structure, but is adapted to the function of each organ. His account of the origin of the fibers of connective tissue from cells, though recently called into question, will, I believe, hold.

One of his valuable contributions is the study of the structure of the heart. He grasped the significance of the work of Krehl, which he said bore the stamp of Ludwig. Krehl demonstrated that when a heart is macerated in a weak acid, the atria can be lifted from the ventricles, thus exposing the atrio-ventricular rings, which are of fundamental importance for a proper understanding of the structure and function of the heart. In other words they are the tendons of origin of the bands of heart-muscle. Dr. Mall saw that this discovery reopened the subject of the architecture of the heart; and that here was a point where progress could be made. In 1900 he gave to John Bruce MacCallum the study of the bands of the heart-muscle. MacCallum unraveled the ventricles of the heart in the embryo pig into superficial and deep spiral bands with their origin and insertion in two tendons, the atrio-ventricular rings and the chordæ tendineæ. As a tribute to this brilliant work, Dr. Mall completed the study on the adult human heart after MacCallum's death, reducing the problem to the following simple terms: To understand the beat of the heart one must figure out how a muscular bag is constructed so as to empty itself. We have Dr. Mall's specimens in the laboratory showing how the spiral cardiac bands contract with each beat of the heart in the exact familiar pattern of wringing out a rag. This prompted Dr. Mall to reconsider the development of the heart, and his work here led to what he considered the next step, that of following out the origin and development of the atrio-ventricular bundle and the Purkinje bands.

Another line of anatomical study which interested him was the study of the brain. Here he has drawn to the anthropological side. He realized that Baltimore afforded a rare opportunity to study the problem of race in connection with the brain. Dr. Hrdlička, the anthropologist in Washington, had said to him that the brain of a negro could be distinguished from that of a white man, and with this in mind Dr. Mall made a comparative study of the brains in the anatomical collection, comparing them by weights, the complexity of their convolutions, the area of the cross-section of the frontal part of the corpus callosum, and other criteria. Realizing that no man can free himself of prejudice, he charted all of his data by means of numbers, filling in the race and sex only after the

charts were complete. In this way he showed that the crude present day methods are inadequate for scientific deductions regarding the relation of the brain to race and sex. Of the criteria on race there remains only the difference in the shape of the brain corresponding to the well-known difference in the shape of the head. He was profoundly interested in the subject of the development of the brain. After the monograph of His on the development of the tracts in the brain written during his last year, Dr. Mall plotted out such tracts as could be made out in the brains of his specimens, and it was, I know, one of his great desires to see this problem developed in the new Carnegie Laboratory of Embryology.

In his anatomical studies Dr. Mall has enriched his science with a wide range of methods. Our laboratory is full of examples of beautiful injections, corrosions of blood-vessels, preparations of connective tissue made by differential digestion and maceration, cleared embryos which show the development of the skeleton, and many others. Through his influence the technique of modelling has been greatly improved and extended. His own methods of work in the laboratory are of great interest, and he frequently discussed the influence of Ludwig in this connection. Contrary to the usual type, Dr. Mall was far more active mentally than physically. I have known him to think and plan with the greatest care so that a bit of routine might be simplified. Thus, it was his habit to think out every detail of an experiment before he undertook it; he never employed the system of trying a thing out without adequate preparation, or of approximating his methods through errors. For this reason he made but one experiment a day. If he failed he would not repeat it until the next day, thus giving himself ample time to think out the reasons of his failure.

He was very intolerant of the collection of unanalyzed material. His interest in technical procedures was only in their bearing upon the solving of problems; it lay in understanding the principles rather than in multiplying evidence.

We have outlined Dr. Mall's work in anatomy as it grew out of his work in Ludwig's laboratory, and we shall sum it up by saying that he approached anatomy with an interest in structure as adapted to function rather than in morphology. But he was not only an anatomist, he was also an embryologist. In 1891, he published an account of a normal human embryo, now placed in the fourth week of development. He made a most careful and accurate study of all its systems, illustrated by the surface form, in models and casts. This was the first human embryo ever modeled in America, and at that time it was the most complete account of any human embryo in existence. In this study he announced several discoveries. He described a new stage in the development of the brain and its nerves, and traced the origin of the splanchnic nerves. Here also was repeated one of Dr. Mall's earlier discoveries, namely that the Eustachian tube and middle ear arise from the first branchial arch, and in this study lay the foundation of his studies on the colon and the vascular system. The effect of this work on Dr. Mall is to be seen in these words in one of his publications: "I always think in human anatomy in relation

to this embryo." Huber has said that this study has served as a model for all future work of its type. It did more, for like his work on the stomach, it represents, as it were, Dr. Mall's program in embryology. Here one can see the beginning of the type of embryological work which will be associated with his name.

This specimen forms the foundation of the priceless collection of over two thousand human embryos which Dr. Mall later gave to the Department of Embryology of the Carnegie Institution of Washington. It was perfect, beautifully fixed and sectioned. When he had finished the description of it he offered it as a tribute to his teacher, His. His returned it, with several others of his own, expressing the wish that they might be the nucleus for a much larger collection. How richly has this gift borne fruit in the development of the science of embryology!

In the study of embryonic development three names stand out in logical sequence, von Baer, His, Mall. Neither His nor Dr. Mall were concerned with the phenomena of maturation, fertilization or the cleavage stages, in the development of the embryo, but the latter has characterized the work of His as laying a foundation for histogenesis. In like manner the work of Dr. Mall in normal embryology may be summed up in the term organogenesis. He has traced the growth of organs up to their adult stage. He has laid the foundation for a complete anatomical survey of the human embryo in all stages of its development. Here, for example, belong his studies on the diaphragm. Based on the discovery of His that the diaphragm arises in the head, in the septum transversum, and shifts caudalward, Dr. Mall determined the origin of the pleuro-pericardial membranes and the pillars of the diaphragm, and then traced the shifting of the diaphragm to its final position in the adult. The same type of work is seen in the study of the ventral abdominal walls, following the shifting of the rectus muscle, and still more clearly is it brought out in his study of the loops of the intestine. He followed the pattern and position of these loops, first in their early shifting from the *cœlom* into the cord, and subsequently studied the mechanism of their return back into the abdominal cavity as the *fœtus* develops. In the dissecting room he determined the normal position of the loops in the adult, and by experiments on animals showed that both the intestine and the omentum seek their normal position when disturbed. Of this work His wrote:

Your satisfaction in your work will be lasting, because you have brought light into a field which was so obscure. The thing which has been lacking in all of our studies on development up to this time has been observations on the transition between the early embryonic and fetal stages up to the form of the adult. For the intestine you have given the entire study from the beginning up to the end, and I regard it a great step in advance.

It is in connection with the development of the vascular system that Dr. Mall made some of his most significant contributions to embryology. One of the most important points in the study of the embryo mentioned above was solving the problem of the primitive ventral branches of the aorta. This he did by showing that the vessels which are the forerunners

of the *cœliac* axis and superior mesenteric artery arise as far forward as the first dorsal segment, and by indicating the method by which they shift back to their position in the adult. This work has since been repeated with more specimens but not analyzed with more insight. I recall in connection with these more elaborate subsequent studies on this subject one of Dr. Mall's characteristic comments: "I can never become interested in the mere collection of new examples after a principle has once been thoroughly established." It is in his work on the development of the vascular system that his physiological bent and the theories he entertained concerning growth gradually converge. He saw the fundamental significance of endothelium in connection with the vascular system; that blood vessels are not parts of the great system of tissue-spaces, with their slow movement of the fluid contained, but are determined rather by a special smooth lining of a differentiated cell or endothelium. He carried over to embryology the methods of injection of blood-vessels and lymphatics in use for the adult and thereby made possible the study of the spread of vessels in the embryo of his own work and that of his students, as illustrated in the *Manual of Human Embryology*, edited by Keibel and Mall. There is represented the progress which was made by the laboratory under his guidance. He established the method by which it will be possible to give a complete account of the development of the vascular system.

Dr. Mall also discovered the fact, now abundantly confirmed, that endothelium can give rise to the fibers of reticulum. In the study of the vascular system he emphasized again and again the value of the study of the organ as a whole. Trained by the man who invented the microtome and himself making improvements on it, he reacted strongly against those anatomists who study only sections. He was interested in the architecture of an organ; to use one of his own phrases he had "a feeling for a structure." Indeed he has often said that if he were to choose a career again, it would be that of an architect. His gift in anatomy, like the gift of a sculptor or the architect, was the power to visualize structure in three dimensions. Thus one can understand his pleasure in the studies of the architecture of the vessels of organs, given not in indefinite terms but showing the exact pattern of all the vessels, the number and relation, the order of arteries from the main to the terminal branches. Thus he has left to us a rich heritage of corroboration of all of the arteries and veins of various organs which is worthy of a place in the great scientific museums of the world. In the study of the development of the vascular system he, more than any one else, has analyzed the laws of vascular growth as outlined by Thoma.

During the latter part of his life, Dr. Mall became more and more interested in the problems associated with his collection; that is to say, in the type of problems for which institutes for research are founded, and which depend for their solution upon the analysis of a large amount of material and the cooperation of experts along closely allied lines. These problems touch more and more closely the problems of clinical medicine and social welfare. Such, for example, is the study of abnormal embryos, leading up to the analysis of their fre-



quency and causes, the study of tubal pregnancy, the normal curve of growth for the human embryo, the determination of its age, the nature of implantation, and the causes of sterility and abortion. He first became interested in the study of abnormal embryos through separating the normal from the abnormal in his collection. In 1893 he described a specimen, then the youngest in his collection, as a normal embryo of the second week, and later concluded that it was an older abnormal embryo. His first general account of abnormal embryos was in the volume of *The Johns Hopkins Hospital Reports*, published in honor of Dr. Welch in 1900. Eight years later he published a monograph on monsters of which Morgan wrote:

The recent publication by Mall on the causes underlying the origin of human monsters marks an epoch in the study of teratology in this country, for he has treated the subject with a breadth of view and a wealth of illustrations rarely found in the handling of this complex question. Mall has brought to the task a profound knowledge of the older literature of the subject, an appreciation of the most modern results in experimental teratology, and a thorough familiarity at first hand with the subject of human monsters. The physician and anatomist are brought into close touch with the work generally supposed to be outside their proper field; and on the other hand the student of malformations in the lower animals will be made to appreciate the inexhaustible supply of human materials with which the anatomist and physician are familiar.

In this study and in the work of the last six years, Dr. Mall has given a masterly analysis of the causes of monsters. He has shown that from the earliest ages of the world's history the study of monsters has been one of the capital problems of anatomy, medicine and natural history; that the belief in supernatural causes gave way to the theory of maternal impressions, and that this must now give way to a scientific analysis of their causes. Dr. Mall recognized that a few abnormalities, polydactyly for example, are germinal and cannot be produced experimentally; but that monsters are not due to germinal or hereditary causes, but are produced from normal embryos by influences which are to be sought in their environment. The cause of monsters, he has indicated, lies buried in the non-committal term of *faulty implantation*. Thus the study of normal and abnormal implantation of the embryo became one of the chief problems which he proposed to study in the new institute of embryology. In his recent paper on cyclopia he has given a masterly analysis of the recent work in experimental embryology. He showed that as soon as Stockard succeeded in experimenting with eggs in such a way as to produce cyclopean monsters at will, the explanation of the process was at hand; for the work demonstrated that a slight change in chemical environment, acting at a critical time, caused cyclopia. Dr. Mall studied the cyclopean monsters in his collection, one of which is at a stage where a complete analysis could be made, and in conclusion he says: "It seems to me that the studies based upon our collection of embryos, as well as recent investigations in experimental embryology set at rest for all time the question of the causation of monsters. It has been my aim to demonstrate that the embryos found in pathological human ova and those obtained

experimentally in animals are not analogous or similar, but identical. A double monster or a cyclopean fish is identical with the same condition in human beings. In all cases monsters are produced by external causes acting upon the ovum." Thus, most localized abnormalities and monsters, of which he gives a wealth of illustrations, can be traced back to the faulty nutrition of the embryo at early critical stages, and the effects can be followed with every grade of intensity, from complete degeneration of the ovum to monsters which survive to term. One of his most interesting deductions is that in some forms of faulty implantation there results dissociation of the tissues of the embryo, so that they grow exactly as do the cells in experiments with tissue-culture, without the correlating forces which check and integrate the organs in normal development.

It is to my mind a significant example that this work was carried on during the years given to the organization of a new department, that the work of administration was so planned that it did not check research. It is not too much to say that this work of Dr. Mall opens up a whole new field, and that it has already formed a broad foundation on which all future study of abnormalities in development must rest. Such was the work with which he was engaged at the time of his death. In his vision of an institute for embryological research he saw that two great lines of work in which he was most interested could be brought to a successful conclusion within a reasonable limit of time. First, that the full development of the study of organogenesis could give us a completely rationalized anatomy, and that only by completing the story of the development of the organism could we hope to understand its normal structure and its range of variation. Second, that there is a group of problems such as determination of the curve of growth, the study of abnormalities and their causes, normal and abnormal implantation and others which may be grouped together under the study of the laws of growth which lie beyond the powers of a single individual, and are thus only to be attacked through organized research. How often has he said during the latter months of his life, "my work is mapped out for the next ten years." Fortunately in his "plea for an institute of human embryology," and in some unpublished manuscripts some of these plans are recorded, but for the loss of those coming years that would have given us his greatest achievements, those achievements for which his whole life has been the preparation, no philosophy can console us. About a month before his death he put the question to me: "What would you say had been the effect of the Carnegie Institute of Embryology upon this laboratory?" to which I replied: "It has lifted the research of the place from a somewhat amateurish state to a professional state." Never shall I forget the pleasure in his face as he replied, "it is exactly what I wished to do." Such was his aim, such the ideal from which he had never swerved from the very beginning of his career.

No account of Dr. Mall's scientific work is complete without a mention of his contribution in the training of others. It is well known that Ludwig published but little under his own

name, so that as time goes on most of his ideas will live through the works of those he trained. Dr. Mall has done both; what he himself accomplished has just been only briefly recorded from a study of something over a hundred works from his pen. Besides this he has developed in this country what might be termed a school of anatomy, represented by five hundred articles which have appeared from his laboratory. Of teaching he had the highest ideal. He once said, "What higher title could there be than that of a great teacher?" That he himself was one of the world's great teachers will be realized when his influence in the development of medical education in this country is adequately analyzed. To the general problems of education he gave deep thought and great originality. His teaching was characterized by two broad principles, which were followed in his own laboratory: First, that each student should approach his work in the spirit of a discoverer. Second, that since in each class there may be those who are destined to become the intellectual leaders of the next generation, liberty in education is absolutely essential, in order that the strong personality might develop. His own methods of training others were unique—so bound up with his own rare personality that none could copy, and few describe them. He had a gift, perhaps a genius, for stimulating thought. Rarely, indeed, by question; the quiz he never used; it was more in the nature of an occasional suggestion, the acuteness of which impressed one more and more profoundly as one pondered over it. Perhaps his most fundamental quality was his rare generosity which, I am convinced, he would freely ascribe to the influence of Ludwig. I recall distinctly an instance in which a student had worked carefully and accurately with him without, however, understanding the meaning of the value of his observations. The student became discouraged and had decided to give up the work, when Dr. Mall asked for his notes, and later published a very interesting paper under the student's name. This incident is most interesting in connection with one of Dr. Mall's letters, written in the early days of the medical school when he was homesick for the laboratory of Leipzig. He cites therein that before leaving Leipzig he had given some incomplete studies to Ludwig evidently expecting him to use them in his own work, but that Ludwig had added experiments and published them all under Dr. Mall's name. He then concludes: "Can you blame anyone for wanting to return to one who would do things like that?" Ludwig, he wrote, was entirely without selfishness, and when I tried to thank him for all he had done Ludwig replied, "Pass it on." This, indeed, became the great watchword of Dr. Mall's life. Most freely did he give his ideas and his energies to his students. You will find no joint research with his students because all that he gave them he meant to be theirs. He demanded in return the development of high standards of work. In fact, perhaps the most lasting effect which he made upon the minds of his followers was the value of scientific standards and the meaning of ideals in research. He never gave first hand praise; the only encouragement which a pupil received was a genuine interest in his work, but what a rare enjoyment when the teacher discussed with the student his preparation. He

made the rounds of the laboratory nearly every day and gave his staff and his students much of his time. Each one learned that Dr. Mall was sure to come while he was making progress to enjoy it with him, and thus the student came to find enjoyment where Dr. Mall found his—in the work itself. Many of his informal talks in the laboratory were on general topics rather than on the specific development of research, and so general, often so whimsical were these discussions that their meaning was lost entirely upon more than one student.

In the organization of departments there are leaders who train others only in their own problems, giving little scope for independent work. Dr. Mall, on the contrary, was keen to give opportunities to those who could develop an independent line of research. Thus, for example, in his laboratory developed the method of tissue-culture. Again, though his own work did not lead him into the newer fields of cytology, he saw to it that this work was represented in the laboratory. An even more striking example, perhaps, is that he was the first to see that the methods of anthropology might be applied with great value to the study of embryology, hence he brought into the department of embryology professional anthropologists, thereby widening the scope of the science of embryology.

Closely bound up with his own scientific achievements is the part he played in the development of scientific publications in this country. According to his own account, when he started out he hoped that the excellent *Journal of Morphology* would care for all the more complete publications of the laboratory, but it became hampered financially and finally suspended publication in 1903. During a term of years those in the laboratory well remember that he constantly discussed the feasibility of establishing a new journal. At the meeting of anatomists held in Baltimore, in 1900, a committee was formed to launch the *American Journal of Anatomy*, and its first number appeared the following November, 1901. In 1906 followed the *Anatomical Record*, both published first in Baltimore. In 1908, when the *Journal of Morphology* was resumed by the Wistar Institute, Dr. Mall's work on monsters comprised its first number. In carrying out his ideas, however, he worked through others to such an extent that many failed to realize whose was the real directing force. His originality, far-seeing vision and courage for undertaking new enterprises could not be better illustrated than in these journals. More striking still, as a sign of his ideal of developing scientific publications in this country are the new contributions to embryology, published by the Carnegie Institution of Washington.

In his introduction to the article on His, Dr. Mall wrote these words:

The ancient science of anatomy has been perpetuated during many centuries by great men who have dedicated their lives to it. The list is a long one, for the development of the science has been slow and progressive from the earliest ages to the present time; we find in it, on the one hand, some of the names of the greatest who have ever lived—Aristotle, Vesalius—on the other, the names of those who rank as leaders of a generation, Bichat, His.

With Bichat and His belongs the name of Mall. His name will be associated with the present strongly physiological bent of modern anatomy, with the laying of a broad foundation of organogenesis in embryology, whereby anatomy is being rationalized, and with the vision of a broadening of the scope of embryology so as to bring it into relation with the problems of clinical medicine and social welfare. In America his place is unique, it goes without saying that he was our greatest anatomist. More than any other man in American medicine he has led his generation into the way of research.

## PUBLICATIONS OF

FRANKLIN PAINE MALL, A. M., M. D., LL. D.,

*Late Professor of Anatomy, Johns Hopkins University*

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## IN MEMORIAM

EDWIN S. LINTON

Edwin S. Linton, a member of the class of 1918 of The Johns Hopkins Medical School, died in France on November 4, 1917. He was a son of Professor and Mrs. Edwin Linton, of Washington and Jefferson College, and a native of Pennsylvania. He graduated at Washington and Jefferson College in 1913 and, after a year of post-graduate study at the same institution, entered The Johns Hopkins Medical School in 1914, where he was an earnest and enthusiastic student until he became a member of The Johns Hopkins Hospital Unit and went to France. At first he was assigned to service at a port hospital for two months as a night superintendent, an admitting officer in the out-patient department, and in the operating room.

Later, he rejoined the staff of the base hospital. After serving in various capacities, he finally was assigned to the medical service as an acting interne.

Upon November 10, 1917, he fell ill with scarlet fever and died, four days later. His death was felt keenly by all, and especially by his classmates and associates, with whom he was a great favorite by reason of his ready wit and optimistic temperament.

Flowers were sent by officers, nurses and fellow students. He was laid to rest on November 15, 1917, with full military honors in the little French cemetery near Base Hospital No. 18.

LYLE BARNES RICH

Lyle Barnes Rich, a member of the class of 1918 of The Johns Hopkins Medical School, died of disease on December 8, 1917, at Base Hospital No. 18, American Expeditionary Force, France, in his 26th year. He was one of a group of 34 medical students who went to France in the summer of 1917 in connection with The Johns Hopkins Hospital Unit.

He was a native of Minnesota, a graduate of the University of North Dakota, and a student at The Johns Hopkins Medical School since 1914. He was an excellent student, being thorough and painstaking in all his work. Although quiet

and reserved by nature, he was a sympathetic friend and wise counsellor to such as were in need of advice or assistance. He had an intuitive knowledge of human nature and a keen perception of character. He was fond of reading, of poetry, and also of music. He was a church member and a consistent Christian.

While in France, he was for the most part assigned to laboratory work, largely in blood determinations and serum reactions, and proved himself to be a careful, painstaking and reliable observer. He was buried in the little hospital cemetery in France with military honors, attended by the whole personnel of the Unit, by the side of his classmate, Edwin S. Linton.

MIRIAM E. KNOWLES

Miriam E. Knowles, daughter of Mr. and Mrs. Thomas C. Knowles, of Yardley, Pennsylvania, died November 12, 1917, at Base Hospital No. 18, American Expeditionary Force, of scarlet fever, after an illness of five days.

Miss Knowles was a graduate of Wellesley College and of The Johns Hopkins Hospital Training School for Nurses, class of 1916. She was an enthusiastic member of The Johns Hopkins Unit, interested in her work, and devoted to her patients; and they to her. Each day in her round of duties, she seemed to find another reason why she was glad to be considered among the first on duty in France, ready to serve her country.

She was buried with other Americans in a little French cemetery very near Base Hospital No. 18. Simple, but impressive, ceremonies were conducted by a clergyman connected with the Y. M. C. A. "Lead Kindly Light," the most loved of hymns, was beautifully sung by a quartette of medical students. The nurses attended in Red Cross uniforms. The officers acted as pallbearers, with the entire personnel as escort. Her casket was draped with the American flag. There were many floral offerings from nurses, officers, students, and her friends among the patients. Every possible honor was shown her as she was laid to rest by those who had learned to know and appreciate her for what she was—a loyal friend and a devoted, conscientious nurse, who had given her life for her country.

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Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

The Nuclei Tubercis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D. Price, \$1.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

## NOTES ON NEW BOOKS.

*The Pathology of Tumors.* By E. H. KETTLE, M. D., B. S., Lond. Cloth \$3.00. (New York: Paul B. Hoeber, 1916.)

This small volume will be appreciated by the student of microscopic surgical pathology who may easily, to say the least, be perplexed by the mass of diverse, uncorrelated nomenclature which abounds concerning tumor pathology. Adoption of the older nomenclature seems not unwise, since a knowledge of synonyms cannot be avoided and the older terms may better be learned first.

The number and quality of the microscopic illustrations in themselves make the book desirable and valuable; whereas its brevity does not bar its usefulness as a handy volume of reference. Its avowed almost total abstinence from reference is regrettable. The value to the student of such a book, in which some concrete idea of the structure of almost any given tumor is quickly to be visualized, would certainly be greatly enhanced if there were present a list of the related noteworthy publications. The scope of such a book as this can only be to furnish nuclei for more complete units of information. The fact, as the author notes, that Durante first enunciated the theory of embryonic rests, usually attributed without qualification in this country to Cohnheim, would be made of more interest to the student if the reference were at hand. This is a less vital instance of the failure of this time-saving plan of little or no bibliography.

The management of the subject matter is simple. In the first part is placed a summary of the various phases of the general biology of tumors; next the general, and thirdly the special pathology of tumors receives attention. The description is clear and concise. However, the notice given certain glands, for instance, the pituitary, is far too scanty. The book fills a niche in the domain of *surgical or tumor pathology* reference books, although its limitations are easily seen. Not the least of the latter is its almost total omission of macroscopic considerations. It is, however, an efficient presentation of many of the "chief points" of microscopic tumor pathology, and should be a handy book for every second and third year student. W. C. D.

*Finch and Baines: A Seventeenth Century Friendship.* By ARCHIBALD MALLOCH, B. A. (Queens); M. D. (McGill); Temporary Captain, Canadian Army Medical Corps. (Cambridge: At the University Press, 1917.)

This charmingly written and beautifully printed quarto of 89 pages, with 9 full-page photogravure illustrations, owes its inception, if we are to credit the author, to the suggestion of Sir William Osler, who has given such an impetus to medical biographical studies in America and England. The lapse of years does not render it difficult for the writer of this brief review to remember "Archie Malloch" as a boy under surgical treatment at The Johns Hopkins Hospital, and to recall his acute mind and his keen interest in the better forms of literature. It is not strange that in after years he should have developed a fondness for the studies which have given us this volume.

The Seventeenth Century Friendship relates the story of the intimacy between Sir John Finch (1626-1682) and Sir Thomas Baines (1622 or 24-1680). Both were medical men and graduates of Cambridge University, which in the troublous times of the period seems to have been preferable to Oxford as a place of study. Both journeyed to Italy together and spent some years at Padua and received degrees there. They later resided at Pisa, where Finch occupied the Chair of Anatomy in the university there under the patronage of the Grand Duke of Tuscany, and remained several years. He had as associates such men as Malpighi, Steno, Borelli and other famous names. Upon Finch's return to England he was made a physician to the Queen, was knighted by Charles II in 1661, and later sent as an ambassador to the Duke of Tuscany.

His friend Baines was also subsequently knighted, and appointed a professor of music at Gresham College. Both Finch and Baines were among the original charter members of the Royal Society of England.

Notwithstanding a decided scientific attitude of mind towards natural phenomena, Finch was not always free from a certain amount of unscientific credulity. He believed that on one occasion a shower of wheat occurred in Italy, and also that the pictures on the walls of a church on certain feast days descended from the walls of their own motion. He also became interested in the case of a blind man in Holland who claimed to have the ability to detect color by touch. Finch seems to have had a degree of incredulity about him, but does not avow his utter disbelief in the possession of such power. The friendship of Finch and Baines seems to have been most intimate. Baines accompanied Finch to Constantinople when the latter was made ambassador, and died there; his remains were brought to England by Finch on his return.

Finch never married, it is thought, out of consideration for the wishes of Baines. The friendship between the two was most cordial and each seems to have supplemented the qualities of the other. Neither were great physicians or investigators, but both were interested in studies which were common to medical men at those times. They were eager for curious bits of natural history and semi-scientific knowledge. Finch seems to have been the best anatomist and man of science; Baines, on the other hand, was the better philosopher and broader thinker. The letters so freely printed which passed between Finch and his sister, Anna Conway, and other relatives threw much light upon contemporary history, manners and customs. The volume also shows the debt of English medical study, especially in anatomy and chemistry, to Italy in the 17th century. The author deserves great praise for the painstaking and admirable use which he has made of his materials.

H.

*A Text-Book of Nervous Diseases for Students and Practising Physicians.* In thirty lectures. By ROBERT BING. Translated by CHARLES L. ALLEN. Cloth. (New York: Rebman Company, 1915.)

As the translator states in his preface, this is a thoroughly useful, practical and up-to-date book. Both the student and the practitioner should find it so. In size between the summary compends and the larger handbooks, it is convenient to handle, the type is good and the illustrations are excellent.

The subject matter is well arranged and well presented. It would be even more attractive had the translator followed less closely the original German phraseology.

The nervous manifestations of arteriosclerosis are especially well treated. T. P. S.

*Diseases of Occupation and Vocational Hygiene.* Edited by GEORGE M. KOBER, M. D., and WILLIAM C. HANSON, M. D., with illustrations and reference tables. Cloth \$8.00. (Philadelphia: P. Blakiston's Son & Co., 1916.)

No one connected with an active out-patient clinic in a large manufacturing community can fail to be impressed with the frequency with which occupational diseases are met with, owing to the fact that very often adequate protective measures are not instituted in many manufacturing establishments. Fortunately, the more enlightened manufacturers are gradually becoming alive to the importance of protecting their workmen against intoxications of various kinds, partly from humanitarian motives and partly owing to the fact that failure to do so has taught them that they lessen the industrial efficiency of their employees. This volume



is, therefore, very timely, since it brings up to date the knowledge that has been acquired concerning the various occupational diseases, as well as the best measures for preventing them. No dispensary, public health official, social worker, corporation surgeon, or director of a manufacturing plant, where the health of its employees is endangered, should be without this modern treatise.

The editors, the senior member of whom has done so much for the furtherance of industrial hygiene in this country, in a preface note, give a most interesting historical account of what has been done up to the present time towards preventing industrial diseases among workmen engaged in menacing occupations. England was the pioneer nation to grapple with this important problem, followed by France, Germany and the United States. Much useful legislation has been enacted in these countries to lessen the menace from various dangerous trades.

The work is really a collection of monographs by specialists in their particular lines. The authors are John B. Andrews, Irene O. Andrews, George L. Applebach, Bailey K. Ashford, Clarence J. Blake, John T. Bowen, Louis Casamajor, C. H. Crownhart, Luigi Devoto, Seward Erdman, Langdon Frothingham, Alice Hamilton, Emery Hayhurst, Charles R. Henderson, Frederick L. Hoffman, Frederick S. Lee, Thomas S. Lee, Thomas M. Legge, Harry Lillenthal, Owen R. Lovejoy, Sir Thomas Oliver, Thomas Ordway, Harry C. Solomon, Elmer E. Southard, Ludwig Teleky, John W. Trask, Ernest E. Tyzzer, George C. Whipple and H. V. Würdemann.

The editors have divided the subject matter into three parts.

Part I deals with the specific and systemic diseases of occupation, including fatigue and the neuroses.

Part II deals with the causation and prevention of occupational diseases and accidents.

Part III is intended to be of service to those who may be called upon to investigate in the shop or factory, and in the dispensary and hospital, the relations of occupation to disability and disease.

For two decades Thomas Oliver's "Dangerous Trades; The Historical, Social and Legal Aspects of Industrial Occupations as Affecting Health" has served a most useful purpose as a work of reference. The present work, to which Sir Thomas Oliver is a contributor, brings our knowledge of occupational diseases thoroughly up to date.

T. B. F.

*Some Personal Reminiscences of Dr. Janeway.* By JAMES BAYARD CLARK, M.D. (New York: G. P. Putnam's Sons, 1917.)

This tribute to the late Dr. E. G. Janeway by an intimate friend is marked by a sincere desire on the part of the author to portray him as he knew him in his daily life in contact with patients and students, and in his professional studies and public life. Dr. Clark gives many interesting reminiscences of acts of kindness towards the sick and deserving, and anecdotes of a personal character showing Dr. Janeway's manner of life and modes of thought. He was kind in his relations with young and inexperienced physicians; he loved his profession, and was high-minded in the performance of all duties; he strove to advance the science of medicine by his labors and studies. The gratitude of the author to Dr. Janeway is most creditable, and forms in reality the key-note of the little book.

*The Obstetrical Quiz for Nurses.* By HILDA ELIZABETH CARLSON. Cloth \$1.75. (New York: Rebnan Company, 1915.)

In writing this "monograph on obstetrics" the author has placed before pupil nurses the first obstetrical quiz compend written for their special needs. For some time the necessity for such a book has been apparent and this work is an excellent attempt to supply this need. In the instructive question and answer form it covers the essentials of obstetrical anatomy, physiology, and pathology. A very good feature is the attention given to the

proper methods in emergencies arising in obstetrical practice at homes.

The chapters on anatomy, physiology, and normal labor are especially well written and the lists of supplies given in Chapter VI should prove of great value to nurses undertaking the care of obstetrical patients at home. The chapter on the new-born child is valuable, as the average nurse knows far too little about the less important of her two patients.

There are a few undesirable features about the book. The advice to nurses to attempt replacing a prolapsed cord by intravaginal manipulations is not good. The two last chapters on anaesthesia seem uncalled for and out of place in the book and it is to be hoped that they will be omitted from future editions. The first of these on scopolamine-morphine anaesthesia is admittedly a copy of the report of Rongy and Arluck published in the New York Medical Journal in September, 1914, and its presence in this book will doubtless be of assistance in the propaganda for "twilight sleep," a procedure that has been given up almost entirely. The last chapter on nitrous oxide anaesthesia is compiled from the reports of several men and is the poorest part of the book.

Although a casual reader may think this book too voluminous and condemn it because of much detailed matter, it is this very attention to minutiae that should make the obstetrical quiz of invaluable assistance to the obstetrical nurse.

J. G. M., Jr.

*Operations on the Bones, Joints, Muscles and Tendons.* By ROBERT SOUTTER, M.D. Cloth \$4.50. (New York: The Macmillan Company, 1917.)

This book considers the various orthopaedic procedures, regionally, in a very satisfactory way. The methods outlined are given completely and in great detail. The cuts are diagrammatic and clear, not handicapped by any attempt at artistic display. The book is extremely well gotten up for the "occasional orthopaedist."

Certain general procedures are repeated in detail each time reference is made to them, as in arthroplasty, overlapping fractures, methods of drainage, etc. This seems unessential.

There seems to be too much emphasis laid on the use of silk as tendon extensions in muscle transplantations, as, for instance, at the knee, where the hamstrings may be anchored directly to the patella, avoiding the complicated technique of silk extension to the patella and tibia.

I. Z.

*Embryology, Anatomy, and Diseases of the Umbilicus, Together with Diseases of the Urachus.* By THOMAS STEPHEN CULLEN, Associate Professor of Gynecology in The Johns Hopkins University and Assistant Visiting Gynecologist to The Johns Hopkins Hospital. Illustrated by MAX BRÜDEL. (Philadelphia and London: W. B. Saunders Company, 1916.)

The delay in giving an earlier review of this monumental work, due to unforeseen, regrettable and irremediable accidents, renders a fresh detailed review unnecessary now. The book bears lasting testimony to the ability, scientific zeal and great industry of the author, who has performed his self-appointed task so well that one feels that the same intensive work will never need to be done again. The volume is an exhaustive presentation of a group of hitherto obscure diseases, and contains 680 pages with 269 figures in the text and 7 full-page illustrations.

It seems, however, to the reviewer a fitting time to add for the benefit of the readers of the BULLETIN, many of whom are especially interested in the work and its author, extracts from some of the reviews which have appeared elsewhere, as showing the reception accorded to it by surgeons and pathologists.

The *Lancet*, London, says: "This book, however, deals not only very fully with all the known diseases of the navel, but also with such other matters as the omphalomesenteric duct and vessels, Meckel's diverticulum, and the urachus. The importance of

the embryology of the umbilicus is very considerable because so many of the lesions are due to a partial or complete lack of closure of the omphalomesenteric duct or of the urachus. The section devoted to this subject is extremely clear, and is illustrated by a very fine series of drawings by Max Brödel. The many interesting and instructive points which a detailed study of the anatomy reveals are well set out in Chapter II, and the four plates showing the different forms of the umbilicus will be a revelation to those who have never studied this region particularly. Umbilical infections and hemorrhage in the new-born child happily have lost the importance they once had, but an account of many of the old epidemics is given by the author and their relation to infections of the umbilical stump clearly shown. A large number of cases of the curious tumors, formed by remnants of the omphalomesenteric duct, the so-called umbilical polyp, are collected and given in full, while the chapters dealing with a patent omphalomesenteric duct and prolapse of the bowel through such a duct are most interesting. As the author rightly points out, when a small umbilical polyp is noted after the cord has come away, the probable persistence of other portions of the omphalomesenteric duct, such as a Meckel's diverticulum or a cord from the mesentery to the umbilicus, must be remembered, and the added possibility of intestinal obstruction developing later in life explained to the parents. It is interesting to find that most of the cases of so-called dermoids of the umbilicus turn out on further investigation to be nothing more than inflammation due to the irritation of an umbilical concretion, the presence of caseous material and wool from the patient's clothing having led to an erroneous diagnosis in many of the cases. Records of cases of Paget's disease, diphtheria and syphilis of the umbilicus are given, and also numerous cases illustrative of the escape of intra- and extra-abdominal fluid, mostly pus, through the umbilicus as well as cases of umbilical fistulae.

"Among the most curious of all the conditions described is the series collected by Dr. Cullen of umbilical tumors containing uterine mucosa or remnants of Müller's duct, in reality adenomyomata of the umbilicus. It was a case of carcinoma of the umbilicus which first led the author to a study of the whole subject, and the chapter on that condition contains the records of many cases of both primary and secondary carcinoma of this region."

The *Edinburgh Medical Journal* says: "The author confesses that up till the year 1904 he had thought that hernia was practically the only lesion to be noted in this locality. A chance case of cancer of the umbilicus, which he happened to meet with in his practice, sent him to the library in search of any records extant of a similar condition. He was astonished at the wealth of material on the umbilicus which he found scattered throughout the literature of surgery, and decided to collect and analyze it. The result of his labors astonishes us. His investigation has been most thoroughly done—the mere assembling of the literature to the end of 1912 took three years—and, with the aid of a number of collaborators, he has summarized what had been written up to that date so completely that no one need go further than his pages to find the gist of what has previously been written on the subject."

"With the aid of a series of excellent diagrams made by Max Brödel the description of the embryology of the umbilical region is rendered perfectly clear, and the understanding of the various congenital defects that are later described is greatly facilitated. The section on the anatomy of the umbilicus is illustrated by four plates containing 60 drawings of 'normal umbilici,' no two of which bear more than a superficial resemblance to one another. In fact, the differences are so marked that it is difficult to conceive a normal type. The author, indeed, has had to divide them into no fewer than nine groups."

"A chapter is devoted to umbilical infections in the new-born, each form of infection being illustrated with notes of a few

typical cases. Umbilical hemorrhage is dealt with in a most instructive and useful way. The numerous conditions associated with aberrations of the omphalomesenteric duct are fully described and profusely illustrated, as are also those of urachal abnormalities. Among other chapters of real clinical value are those on umbilical concretions, tumors and infective granulomata.

"As we have already indicated, this work represents an enormous amount of literary research, as well as pathological and clinical observation, and it forms a valuable source of reference."

The *American Journal of Obstetrics and Diseases of Women and Children* says: "It represents the result of eight years of intensive and scrupulously careful research work. The assembling of the literature of the subject alone and its critical study took all of three years, and was made possible only by the facilities of the Surgeon-General's Library at Washington. As an example of the care taken in its production, when the book was set up in galley, the author, realizing that the tremendous number of cases mentioned would be most valuable with the fewest chances of error, had the entire book checked off with the original articles. Subsequent writers can accordingly feel safe in relying on the accuracy of the cases recorded."

The *Boston Medical and Surgical Journal* says: "It constituted a really complete survey of the literature upon the umbilicus and urachus, with the exception of umbilical hernia, and this survey is enriched with a large amount of original observation. Three-quarters of the volume are devoted to the umbilicus, one-fourth to the urachus, and the whole profusely illustrated with 269 text-figures and 7 plates, many of them original and some colored. The work is one of the best Teutonic type of thoroughness and value, written by an American in a charming and delightful English literary style, unusual among physicians."

The *American Journal of the Medical Sciences* says: "Perhaps it is the very portliness of the volume, perhaps it is merely a habit of much writing acquired during its preparation, that inspired the author with the idea of condensing its contents into a preface of some three thousands words. We urgently counsel those who may contemplate, as we fear some hardy souls may, the perusal of the entire volume from cover to cover, to begin systematically with the preface. Then to follow the advice therein to study (not merely to admire) the illustrations of embryology; and then (but this advice is not in the preface) to lay the volume carefully away upon its shelf, to be called upon as a work of reference whenever needed—and this, we predict, will not be very often."

"The plan of the work is all inclusive; embryology, anatomy; umbilical infections in the new-born; remnants of the omphalomesenteric duct; congenital polyps; Meckel's diverticulum; intestinal cysts; umbilical concretions; purulent and fecal fistulae at the umbilicus; umbilical herniae; umbilical tumors; patent urachus; urachal cysts—these are but a few of the chapter headings, for the volume treats *de omnibus rebus et quibusdam aliis*. Not only are the history, the pathology, the symptoms, the diagnosis, the prognosis and the treatment of each condition given at length, but there is appended nearly to every section a long list of case abstracts, alphabetically arranged according to the author's name, which have been disinterred from former and less worthy sepulchers to be reinterred with befitting pomp and splendor in this magnificent mausoleum."

H. M. H.

*Bibliography of William Henry Welch, M. D., LL. D.* Prepared by WALTER C. BURKET, M. D., of The Johns Hopkins University. (Baltimore: The Johns Hopkins Press, 1917.)

This attractive volume of 47 pages has been prepared by Dr. Burkett as a part of a larger scheme to collect and publish the papers of Dr. Welch scattered throughout the medical literature of the world. This remarkable collection of titles shows how much



material is at present buried in periodicals, transactions, reprints or manuscripts which deserves publication in a collected form readily accessible to students and teachers of medicine. The preparation of this volume has involved much care and painstaking search on the part of the compiler, who deserves the thanks of all physicians for his altruistic labors. After an examination of the wealth of material to which it is an index, one feels that the publication of the larger collection ought not to be indefinitely delayed.

H. M. H.

*International Clinics: A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles on Treatment, Medicine, Surgery, Neurology, Pediatrics, Obstetrics, Gynecology, Orthopedics, Pathology, Dermatology, Ophthalmology, Otolaryngology, Rhinology, Laryngology, Hygiene, and other Topics of Interest to Students and Practitioners.* By Leading Members of the Medical Profession throughout the World. Edited by H. R. M. LANDIS, M. D., Philadelphia, U. S. A. (Philadelphia and London: J. B. Lippincott Company.)

Owing to the great variety of the papers in the rapidly recurring volumes of the international clinics, it is not practicable to give any review in detail of them. The papers vary, it is true, in excellence and execution, but all make special appeal to some members of the medical profession, and hence are of value. The titles mentioned below, however, will give some conception of the scope of the papers and the appeal to one reader at least.

#### 26TH SERIES, 1916, VOLUME IV.

- "Insomnia as a Dread," by James J. Walsh, M. D., New York.
- "Duodenal Ulcer in Infancy," by Henry F. Helmholtz, M. D., Chicago, Ill.
- "The Psychology of the Criminal under the Sentence of Death," by Paul E. Bowers, M. D., Michigan City, Indiana.

#### 27TH SERIES, VOLUME I.

- "The Tangled Skein," by J. Madison Taylor, M. D.
- "Health Efficiency of Workers Due to their Living Conditions," by H. R. M. Landis, M. D.

#### 27TH SERIES, VOLUME II.

- "Gout and Infectious Arthritis," by Henry A. Christian, M. D.
- "Typhoid Fever with Complications," by Lewellyn F. Barker, M. D.
- "Jaundice with Enlarged Liver in a Young Adult," by Thomas McCrae, M. D.
- "A Group Study of the Results of One Hundred Physical and Mental Examinations of So-Called Well Children," by William R. P. Emerson, M. D.
- "Skin Grafting" by Arthur M. Shipley, M. D.
- "Giovanni Maria Lancisi (1654-1720)," by John Foote, M. D.

#### 27TH SERIES, VOLUME III.

- "Concerning the Etiology of Iridocyclitis, with Special Reference to Local Infections," by George E. de Schweinitz, M. D.
- "Chronic Nephritis, with a Discussion of Functional Tests," by Henry A. Christian, M. D.
- "Lectures on Intracranial Hemorrhage," by Charles Greene Cumston, M. D., Geneva, Switzerland.
- "A Study of Arterial Blood Pressures, with Reference to their Clinical Values," by Thomas E. Satterthwaite, M. D.
- "Neurasthenia Before and After the War," by James J. Walsh, M. D.

- "Observations Regarding the Operative Treatment of Selected Cases of Cerebral Spastic Paralysis Due to an Intercranial Hemorrhage at Birth," by William Sharpe, M. D.

#### 27TH SERIES, VOLUME IV.

- "Compound Comminuted Fracture of the Tibia and Fibula from Railroad Injury, etc., by Arthur Dean Bevan, M. D.
- "Two Lectures on Injuries to the Cranium and the Brain in Warfare," by Charles Greene Cumston, M. D.
- "Some Food Facts for War Time Consideration," by Gordon J. Saxon, M. D.

*Clinical Cardiology.* By SELMAN NEWHOFF, B. S., M. D. Cloth \$4.00. (New York: The Macmillan Company, 1917.)

As its name indicates, "Clinical Cardiology" is written primarily from the clinical standpoint. The first third of the book, which deals with the anatomy and physiology of the heart, instrumental methods of examination, and the arrhythmias, is concise, though this conciseness leads at times to a somewhat dogmatic treatment of controversial matters, as for instance, the description of the course of the excitation wave in the ventricle. The experimental and pathological work on which the interpretation of graphic records is based, receives scant attention. The portion dealing with the arrhythmias is profusely illustrated, clear, and up to date. The passage on the displacement or hypertrophy of the heart, and the form of the electrocardiogram are excellent, and the author's views on splitting of the P and R waves are of interest. Throughout this portion of the book care is taken to correlate clinical signs with graphic records.

The chapter on orthodiascopy is much needed. Perhaps the most valuable part of the book is that on physical examination, on which are brought to bear a great many resources not commonly appreciated. The author's distrust of percussion outlines will be shared by all those who have access to the X-ray even if his "rational method" fails, because of its indirectness, to meet with favor.

The chapters on endocarditis, myocarditis and cardiac syphilis embody much valuable material, formerly accessible, if at all, only with difficulty. That on myocarditis and coronary sclerosis has the same merit and is probably as clear as the present state of our knowledge on these subjects will admit. Intraventricular conduction defects might have well been mentioned in this connection. Recent attempts at exact measurement of the cardiac reserve are dismissed in a page, as inferior to general clinical observations before and after exercise, yet at least one such measurement promises to be of value, namely, Peabody's estimation of the cardiac reserve by means of the vital capacity of the lungs. The remainder of the book is devoted to miscellaneous topics, cardiotherapy, renal tests in cardiac disease, the management of cardiac disease, blood pressure, weak heart, precordial pains, and therapy of the circulation in pneumonia.

The arrangement of the book might be improved, in spite of the difficulty caused by the variety of topics necessarily included. A fairly extensive bibliography with few important omissions is appended to each chapter, which would have been more useful but for the conspicuous lack of references to specific authors throughout the text. Those who desire a detailed knowledge of the physiology of the heart, normal and pathological, or of its pathological lesions will fare better elsewhere. Those who appreciate the work of a keen and original clinical observer on the circulation as viewed from the clinical standpoint, with sufficient description of graphic methods to make the volume intelligible, will find it both stimulating and valuable.

H. B. R.



# BULLETIN

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## THE EFFECT OF FORCED FEEDING ON THE NITROGEN EQUILIBRIUM AND THE BLOOD IN PERNICIOUS ANEMIA

By HERMAN O. MOSENTHAL

(From the Medical Clinic of The Johns Hopkins Hospital)

Forced feeding has always been relied on as an important aid in the treatment of pernicious anemia. This form of therapy is based on the common idea that weak and feeble individuals become healthy and strong if they receive a generous amount of nourishing food. Such a conception has no scientific foundation and yet it is the only one on which the present day use of diet in this disease rests. Prolonged feeding experiments in which the diet has been accurately weighed and calculated are lacking and the skepticism of many physicians in regard to the value of diet in pernicious anemia evidently depends largely upon circumstantial evidence and not upon accurate observations.

If a high diet is to be of benefit to a case of pernicious anemia, it should bring about at least two results: First, there should be an assimilation of protein by the body, or, measured in terms of nitrogen, there should be a positive nitrogen balance; second, the red blood cells and hemoglobin should increase. The present article deals with three cases of perni-

cious anemia who were put on forced feeding for about one month and studied with the above points of view in mind. It was originally intended to make this work much more extensive, but inasmuch as under the present circumstances it will have to be discontinued indefinitely, the cases observed thus far are reported at this juncture, as they prove certain points in regard to the relation of diet to pernicious anemia.

Some doubt still exists as to whether or not it is possible to effect an assimilation of protein in pernicious anemia and allied conditions. Pearce (1) has recently made the following excellent summary of the status of this question:

From a review of the literature it is evident that in anemia, with or without splenic disease, the majority of investigators have experienced difficulty in obtaining a nitrogen balance. Umber (2), in his study of Banti's disease; Minot (3), in pernicious anemia; McKelvy and Rosenbloom (4), in congenital hemolytic icterus, and Rosenqvist (5), in pernicious anemia and bothrioccephalus anemia, all report a pathologic destruction of protein. Umber (6) goes so far as to urge this "toxic destruction" as a

criterion for operation. Von Noorden (7) alone opposes this theory of increased destruction of protein in anemia. In the two cases we report, no difficulty was experienced in obtaining a positive nitrogen balance before operation: feeding was not forced, the patients merely satisfying their natural desires for food. Nevertheless, the increased retention, immediately after the operation, on the same nitrogen intake would appear to support the theory that some toxogenic influence had been removed. To this influence, however, must be added as a cause of retention the higher level of reparative processes going on in the body; as, for example, in the bone marrow and possibly other organs. It is, however, difficult to reconcile our slight positive balance with Umber's marked negative balance, before operation.

The cases to which Pearce refers, as exhibiting a positive nitrogen balance, are one of congenital hemolytic icterus (8) and one of pernicious anemia (9). In neither instance was there more than a slight positive nitrogen balance before splenectomy and in the case of pernicious anemia, some time after the operation, there was no increased assimilation of nitrogen. Both cases were studied for short periods only. It may be concluded, therefore, that a markedly positive nitrogen balance has not as yet been observed in pernicious anemia.

The following cases of pernicious anemia were put on high diets. The food was made as appetizing as possible, the personal wishes of the patients were consulted and no attempt was made to maintain a definite proportion of proteins, fats or carbohydrates. It is notoriously difficult to administer large quantities of food to many cases of pernicious anemia. This problem was encountered only with H. M., Medical No. 37787. However, careful nursing and attention to a moderate degree of myocardial insufficiency finally won the day and this man consumed a fair amount of food, though never with the same relish as the other cases. It is not intended to convey the impression that it has been possible to force feeding in every patient. In fact, G. R. B., Medical No. 36704, after doing splendidly for some time following his discharge from the hospital, threw all precautions to the winds, stopped his hydrochloric acid, indulged in a great deal of alcohol, and finally returned for treatment. After one month's attempt, under ideal conditions, and with the patient's enthusiastic co-operation, it was found impossible to administer a high diet.

These patients were all kept under strict supervision in a small metabolism ward. They remained in bed, thus establishing their metabolic requirements at as low a level as possible. The only medication which they received was dilute hydrochloric acid. In one case transfusions were given. The food values were calculated according to Atwater and Bryant's tables. An actual analysis of a considerable number of samples showed that such calculations were accurate for the food materials used. The nitrogen of the urine and feces was determined by the Kjeldahl method.

The histories and results of observations in these cases are as follows:

G. R. B. Medical No. 36704. Male, white, aged 50.

Diagnosis: Pernicious anemia.

Admitted to The Johns Hopkins Hospital October 2, 1916.

The patient lived in Mississippi up to five years ago, and during that time had chills and fever every year. He complains of weak-

ness and shortness of breath on exertion. He has had numbing and tingling in the legs occasionally, and has noted that his skin has been somewhat yellow.

On admission, he was well developed and nourished but extremely pale. The sclerae had a lemon yellow color. The area of precordial dullness measured 4 x 12 cm. There was a blowing systolic murmur over the entire precordium. The liver was felt one finger's breadth below the costal margin; the spleen was not felt. Otherwise, the physical examination was negative.

On October 3, the red blood cells were 1,216,000, the hemoglobin 28 per cent, the white blood cells 5200, and the differential count was as follows: Polymorphonuclear neutrophils 64 per cent, lymphocytes 16 per cent, large mononuclear cells 7 per cent, eosinophiles 3 per cent, basophiles 1 per cent, myelocytes 3 per cent, transitionals 3 per cent, and unclassified cells 3 per cent. The blood smear showed a moderate variation in size and shape of the red blood cells, with a tendency towards the large type of red blood cell. The red cells were deeply and diffusely stained and no nucleated red cells were seen; there was a slight degree of basophilia, but no granular degeneration. The blood platelets appeared to be decreased.

On October 15, thirteen days after admission, after two transfusions had been given, and the red cells had increased to almost 2,000,000, the forced feeding was begun. The further course of events may be followed in Table 1. During this period he received two additional transfusions, as indicated on the chart, and was taking 20 to 40 minims of dilute hydrochloric acid after meals. No other medication, except an occasional cathartic, was given. The patient was kept in bed while these observations were made.

H. M. Medical No. 37787. Male, white, aged 60.

Diagnosis: Pernicious anemia.

Admitted to The Johns Hopkins Hospital April 14, 1917.

In March, 1915, following an "attack of grippe," he was short of breath and weak. In the spring of 1916, his skin began to burn, itch and tingle. He was very hypersensitive to odors, but nothing abnormal could be found in his nose by specialists. His eyes became weaker and black dots impaired his vision. This condition became worse until at present he can scarcely read more than 15 minutes at a time. In April, 1916, shortness of breath, paleness, jaundice and weakness became so marked that he went to the Bermuda Islands to recover, but obtained no relief. In the winter of 1916-17, he was so weak and short of breath that he could scarcely walk. He went to Florida and his symptoms cleared up to a remarkable degree. Later, he again relapsed and he came to the hospital for treatment. His appetite is very poor and his bowels are constipated.

The patient was extremely pale. There was marked dyspnea even on slight exertion. The skin and sclerae had a lemon yellow color. He was well nourished. There were numerous fresh and old hemorrhages scattered throughout both retinae. The area of precordial dullness extended 3 cm. to the right and 12 to the left. At the apex there was a soft blowing systolic murmur. The second pulmonic sound was louder than the aortic second. The pulse was regular in force and frequency. The rate varied from 80 to 95. The blood pressure was 110 systolic and 60 diastolic. The liver edge was at the costal margin; the spleen was felt one finger's breadth below the costal margin; it appeared to be soft. On April 19 the red blood cells were 1,000,000, the hemoglobin 25 per cent, and the white blood cells 4600. On May 5 the differential count showed 55.6 per cent polymorphonuclear cells, 35.2 per cent lymphocytes, 5.2 per cent large mononuclear cells, 2 per cent transitionals, 1.6 per cent eosinophiles, and 0.4 per cent basophiles. The blood smear on April 18 showed great variation in the size and shape of the red cells; there were many microcytes and macrocytes; the red blood cells were of a dark color and diffusely stained; there was a moderate number of normoblasts and megaloblasts; there was

TABLE 1.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (G. R. B., MED. NO. 36704)

Date	Food					Nitrogen per day, gm.					Blood		Transfusion clotted, blood, c.c.	Weight, kg.
	Protein, gm.	Fat, gm.	Carbo- hydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin per cent		
10-15-16	89.5	128.4	289.9	2750	39.1	10.69	3.18	13.87	14.3	+ .43	.....	..	...	70.3
10-16-16	106.1	159.6	276.7	3054	43.3	8.45	3.00*	11.45	16.9	+5.45	2,016,000	36	...	70.4
10-17-16	103.2	184.1	326.6	3474	49.4	8.53	3.00*	11.53	16.5	+4.97	.....	..	...	70.2
10-18-16	114.5	133.5	353.2	3159	44.8	9.89	3.00*	12.89	18.3	+5.41	.....	..	...	70.4
10-19-16	95.9	183.5	324.4	3430	48.5	10.92	2.13	13.05	15.3	+2.25	.....	..	...	70.6
10-20-16	100.1	139.9	306.3	2967	42.1	7.17	2.13	9.30	16.0	+6.70	1,716,000	36	...	70.4
10-21-16	112.9	201.6	301.1	3572	50.7	12.43	4.24	16.67	18.1	+1.43	.....	..	...	70.4
10-22-16	118.0	177.3	411.0	3818	54.0	9.27	3.79	13.06	18.9	+5.84	.....	..	...	70.6
10-23-16	117.8	172.8	391.0	3693	51.6	13.44	3.02	16.46	18.8	+2.34	.....	..	...	71.3
10-24-16	99.1	132.3	273.2	2757	38.9	13.99	3.02	17.01	15.9	-1.11	1,848,000	36	500	70.7
10-25-16	69.4	86.9	174.0	1806	25.4	7.55	1.61	9.16	11.1	+1.94	2,248,000	39	...	70.9
10-26-16	116.8	161.8	377.1	3130	50.7	12.80	1.61	14.41	18.7	+4.27	.....	..	...	69.6
10-27-16	116.3	202.0	371.8	3880	54.9	12.15	1.61	13.76	18.6	+4.84	.....	..	...	70.6
10-28-16	106.1	206.3	430.3	4063	57.6	10.43	2.98	13.41	17.0	+3.59	.....	..	...	70.5
10-29-16	100.8	160.1	505.3	3974	56.2	9.27	2.98	12.25	16.1	+3.85	.....	..	...	70.7
10-30-16	117.2	160.3	498.3	4014	56.2	10.35	5.22	15.57	18.8	+3.23	.....	..	...	71.3
10-31-16	77.7	127.1	402.9	3152	43.9	8.95	2.17	11.12	12.4	+1.28	2,328,000	39	500	71.7
11-1-16	85.2	149.6	295.9	2954	41.1	11.34	2.17	13.51	13.6	+ .09	2,368,000	40	...	71.5
11-2-16	123.8	165.2	500.0	4094	57.5	11.99	2.17	14.16	19.8	+5.64	.....	..	...	71.1
11-3-16	129.5	180.0	518.8	4332	61.0	9.14	3.45	12.59	20.7	+8.11	.....	..	...	71.0
11-4-16	97.6	183.9	500.0	4160	58.3	11.93	3.45	15.38	15.6	+ .22	.....	..	...	71.3
11-5-16	90.7	121.2	442.9	3315	46.2	9.59	3.45	13.04	14.5	+1.46	.....	..	...	71.7
11-6-16	111.2	157.5	272.4	3038	42.4	13.57	3.45	17.02	17.8	+ .78	3,224,000	45	...	71.5
11-7-16	93.8	150.1	501.6	3837	54.0	11.03	3.40	14.43	14.9	+ .47	.....	..	...	71.0
11-8-16	122.2	164.9	507.8	4117	57.8	10.52	3.40	13.92	19.6	+5.68	.....	..	...	71.2
11-9-16	103.7	160.4	544.5	4149	57.6	9.90	3.40	13.30	16.6	+3.30	.....	..	...	71.9
11-10-16	124.0	220.9	504.1	4630	63.5	6.82	3.45	10.27	19.8	+9.53	.....	..	...	72.8
11-11-16	99.4	139.1	469.2	3625	49.8	10.16	3.45	13.61	15.9	+2.29	2,760,000	48	...	72.8

\*The nitrogen content of the feces was estimated on these days; the remaining figures represent actual determinations.

TABLE 2.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (H. M., MED. NO. 37787)

Date	Food						Nitrogen per day, gm.					Blood		Weight, kg.
	Protein, gm.	Fat, gm.	Carbo- hydrate, gm.	Alcohol, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.	Hemoglobin, per cent	
4-18-17	52.2	84.0	193.8	.....	1790	26.6	7.74	2.00	9.74	8.35	- 1.39	.....	..	67.2
4-19-17	50.9	87.0	144.3	.....	1610	23.8	6.11	2.00	8.11	8.14	+ 0.03	1,000,000	25	67.6
4-20-17	79.3	173.6	258.9	13.9	3097	45.6	5.28	2.00	7.28	12.68	+ 5.40	.....	..	67.8
4-21-17	68.1	137.8	336.8	18.5	3072	44.7	7.06	2.00	9.06	10.89	+ 1.83	1,476,000	28	68.7
4-22-17	83.0	177.7	287.6	27.6	3365	48.4	5.44	1.80	7.24	13.28	+ 6.04	.....	..	69.5
4-23-17	101.5	225.6	267.2	13.9	3706	53.4	Lost	1.80	1.80+	16.24	+14.44	.....	..	69.4
4-24-17	88.8	216.8	339.0	13.9	3867	54.9	8.03	1.80	9.83	14.20	+ 4.40	1,504,000	24	70.3
4-25-17	119.3	224.7	321.8	13.9	3995	56.6	7.39	1.80	9.19	19.07	+ 9.88	.....	..	70.6
4-26-17	111.3	244.4	355.8	13.9	4285	60.7	8.20	1.80	10.00	17.80	+ 7.80	.....	..	70.5
4-27-17	113.3	251.5	362.3	13.9	4386	61.8	6.57	1.80	8.37	18.12	+ 9.75	2,356,000	30	70.9
4-28-17	119.3	245.6	334.1	13.9	4240	59.3	7.44	1.72	9.16	19.08	+ 8.92	.....	..	71.5
4-29-17	122.8	236.3	368.1	13.9	4307	60.6	8.58	1.72	10.30	19.64	+ 9.34	2,308,000	34	71.0
4-30-17	130.9	234.1	372.4	13.9	4338	61.4	8.00	1.72	9.72	20.94	+11.22	.....	..	70.6
5-1-17	115.4	253.5	357.0	13.9	4392	62.3	9.04	1.72	10.76	18.46	+ 7.70	2,224,000	42	70.4
5-2-17	137.3	247.6	309.5	13.9	4232	60.4	9.41	1.72	11.13	21.96	+10.83	.....	..	70.0
5-3-17	123.0	226.4	355.5	13.9	4165	59.3	10.98	2.06	13.04	19.68	+ 6.64	2,670,000	46	70.2
5-4-17	134.0	256.9	317.7	13.9	4338	61.4	10.98	2.06	13.04	21.44	+ 8.40	.....	..	70.5
5-5-17	140.9	250.8	382.1	13.9	4574	64.7	11.13	2.06	13.19	22.54	+ 9.35	3,068,000	46	70.6
5-6-17	123.5	257.9	381.9	13.9	4567	64.4	9.65	2.06	11.71	19.76	+ 8.05	.....	..	70.8
5-7-17	143.0	257.9	348.8	13.9	4511	63.6	10.44	2.06	12.50	22.88	+10.38	2,954,000	48	70.9
5-8-17	153.5	263.1	404.9	13.9	4833	68.2	10.67	2.06	12.73	24.56	+11.83	.....	..	70.8
5-9-17	146.3	261.6	361.6	13.9	4613	64.9	13.25	2.13	15.38	23.40	+ 6.02	2,976,000	52	71.0
5-10-17	157.4	270.3	382.9	.....	4729	66.6	13.17	2.13	15.30	25.18	+ 9.88	.....	..	70.9
5-11-17	151.8	261.4	421.9	.....	4783	66.7	13.32	2.13	15.45	24.28	+ 8.83	.....	..	71.7
5-12-17	128.3	245.1	391.5	.....	4410	61.6	13.07	2.13	15.20	20.52	+ 5.32	3,240,000	54	71.5
5-13-17	146.7	249.2	366.4	.....	4421	61.6	13.46	2.07	15.53	23.47	+ 7.94	.....	..	71.7
5-14-17	152.6	256.7	421.8	.....	4742	66.0	14.95	2.07	17.02	24.41	+ 7.39	3,016,000	55	71.8
5-15-17	156.9	258.2	353.9	.....	4495	62.2	15.20	2.07	17.27	25.10	+ 7.83	.....	..	72.1
5-16-17	168.7	292.3	337.1	.....	4792	66.3	16.56	2.07	18.63	26.99	+ 8.36	3,376,000	57	72.2
5-17-17	151.2	285.6	376.0	.....	4818	67.0	13.16	2.07	15.23	24.19	+ 8.96	.....	..	71.8
5-18-17	153.6	266.7	426.3	.....	4858	66.8	15.62	2.07	17.69	24.57	+ 6.88	3,728,000	60	72.7
5-19-17	166.0	263.3	373.1	.....	4660	64.1	14.47	2.07	16.54	25.56	+10.02	.....	..	72.7



granular degeneration and basophilia, and the blood platelets were diminished.

The patient's symptoms were evidently caused by anemia and insufficient heart action. The only medication which he received was infusion of digitalis and dilute hydrochloric acid. With these aids his dyspnea was diminished and his appetite increased. The diet, the red blood cell counts and the percentage of hemoglobin may be followed in Table 2. His diet was forced as much as possible from April 18 until May 20. During this period he remained in bed. On May 20 he felt so well, the dyspnea, weakness and dimness of vision having disappeared completely, that he insisted on leaving the hospital.

W. B. Medical No. 36933. Male, white, aged 63.

Diagnosis: Pernicious anemia; lobar pneumonia.

Admitted to The Johns Hopkins Hospital September 21, 1916.

The patient was well until two days prior to his admission to the hospital. At this time he had a chill and complained of pain in the back. He was admitted to the hospital in an almost stupor condition and was difficult to arouse. He had been working as sexton in a church until he was taken sick and had been doing fairly hard work.

The patient had the signs and symptoms of a lobar pneumonia in the right lower lobe. These cleared up shortly, so that six days after admission the temperature was normal and all traces of the acute disease had disappeared. The physical examination exclusive of the signs that could be referred to the pneumonia showed that the patient was fairly nourished but was very pale. There was slight edema above the ankles. The sclerae had a lemon tint; there were numerous small hemorrhagic spots upon the retinae. Over the whole precordium there was a blowing systolic murmur which was not transmitted to the left beyond the apex region. The spleen was not felt; the liver was two fingers' breadth below the costal margin. Otherwise the physical examination was negative. On September 21, the red blood cells were 656,000, the hemoglobin was 15 per cent, and the white blood cells 3500. The differential count showed that the polymorphonuclear neutrophils were 60 per cent, the lymphocytes 34.5 per cent, the large mononuclears 3.5 per cent, the transitionals 1.5 per cent, and the basophiles 0.5 per cent. The cells varied very much in size and shape; very many were distinctly larger than normal. There was basophilic and granular degeneration. A few megaloblasts and normoblasts were present.

The patient was transfused twice and given two courses of sodium cacodylate. On November 17, his red blood cells had risen to 3,500,000, and his hemoglobin to 70 per cent. This was almost exactly two months after his admission to the hospital. At that time, forced feeding was begun, the results of which are given in Table 3. During the period of high diet, he was given 20 minims of dilute hydrochloric acid after meals, but no other medication, and was kept in bed.

S. F. Medical History No. 37840. Male, white, aged 38.

Diagnosis: Chronic myeloid leukemia, secondary anemia.

Admitted to The Johns Hopkins Hospital December 17, 1916.

Seven years ago the patient first noticed that his abdomen was increasing in size. He was treated in the University Hospital of Baltimore one year later with X-rays, the diagnosis being splenomyelogenous leukemia. As the result of this therapy the spleen became very much smaller. Two years later he began to take arsenic, which he continued up to one year ago. The tumor in the abdomen has progressively increased in size; there have been frequent nosebleeds. The patient bleeds easily and a small injury will cause a bruise. On November 19, 1916, the patient went to Dr. Kelly's sanatorium, where he took three treatments of radium about 8 to 10 days apart. Under this therapy his spleen shrank markedly and he felt stronger than before. After an interval of three weeks, his gums became swollen and began to bleed. Ten

days ago, epistaxis began and he bled for four days and four nights, losing a great deal of blood. At about the same time, small hemorrhages appeared in the skin. These would soon disappear and be replaced by a new crop.

The patient was well nourished. There was no dyspnea. He was constantly expectorating blood and blood was oozing from the nostrils and the gums. There were numerous hemorrhages in the skin. These were especially marked in the lower extremities. The largest ones were in the back, being 10 x 5 cm. The skin and sclerae had a peculiar orange tint. The heart and lungs showed nothing of note. The liver edge was felt at the costal margin; the spleen was remarkably enlarged, extending to about the level of the crest of the ilium below and almost to the median line on the right. The red blood cells were 3,120,000; the white blood cells 4600; the hemoglobin 30 per cent. The differential count showed polymorphonuclear cells 74.8 per cent, small mononuclear cells 16 per cent, large mononuclear cells 6.8 per cent, transitional cells 0.4 per cent, myelocytes 0.8 per cent, eosinophiles 0.4 per cent, and basophiles 0.8 per cent. Before radiation the blood count had been: Red blood cells 2,984,000; white blood cells 160,000; hemoglobin 52 per cent; and the differential count: Polymorphonuclear neutrophils 20.7 per cent, small mononuclear cells 10.0 per cent, large mononuclear cells 2.3 per cent, transitional cells 1.6 per cent, myelocytes 5.5 per cent, basophiles 3.3 per cent, and eosinophiles 3.6 per cent.

From December 17 to March 2 numerous transfusions were given, and arsenic therapy was employed. There was no improvement; the bleeding from the nasopharynx, which continued during this period, finally resulting in a very severe secondary anemia. The blood platelet count was very low; the blood clot did not contract but was typical of a clot deficient in blood platelets. A marked leucopenia accompanied this secondary anemia. There were several retinal hemorrhages and marked bleeding from the gums. Hemorrhages into skin were present to only a very slight degree. On March 2 the red blood cell count was 912,000, the hemoglobin 20 per cent and the white blood cells 1350. On this date forced feeding was begun, the hemorrhages ceased, and the further course of the patient can be followed in Table 4.

It is very evident from the study of the figures as given in Tables 1, 2 and 3, that there was no difficulty encountered at any time during the observation in bringing about an extensive assimilation of nitrogen. In the case of G. R. B., Table 1, the only patient in whom transfusions were employed, it may be noted that following each of the transfusions there was a lowered nitrogen balance. This was only to be expected, inasmuch as the nitrogen contained in the transfused blood was not included in the intake. This result would indicate that much of the protein material contained in the blood introduced intravenously was lost in the urine. The positive nitrogen balance diminished considerably a few days after the second transfusion. The patient did not consume as much food on some of these days, and it is very difficult to ascertain the exact reasons for these fluctuations. The other two cases, who were not transfused (Tables 2 and 3) certainly exhibited a much steadier positive nitrogen balance. The amount of nitrogen and the caloric value of the diet may possibly be most readily appreciated from the summary given in Table 5. One of these patients retained 3.4 gms. of nitrogen a day for 28 days, another, 3.4 gms. a day for 32, and the third 6.8 gms. a day for 36 days. These are very large positive balances, and there can be no doubt that cases of pernicious anemia can assimilate nitrogen readily if put upon forced diets.

TABLE 3.—RESULTS OF FORCED FEEDING IN A CASE OF PERNICIOUS ANEMIA (W. B., MED. NO. 36933)

Date	Food				Nitrogen per day, gm.					Blood		Weight, kg.	
	Protein, gm.	Fat, gm.	Carbo-hydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.		Hemoglobin per cent
11-16-16	79.9	125.0	230.1	2434	48.9	10.49	0.43	10.92	12.78	+ 1.86	..	..	49.7
11-17-16	80.2	125.2	229.0	2432	49.6	10.06	0.43	10.49	12.83	+ 2.34	3,500,000	70	49.0
11-18-16	79.9	125.7	230.1	2440	49.7	8.21	0.42	8.63	12.78	+ 4.15	..	..	49.0
11-19-16	80.2	124.0	230.5	2427	49.8	11.32	1.58	12.90	12.83	- 0.07	3,000,000	68	48.7
11-20-16	79.0	126.8	400.2	3144	63.6	10.56	1.58	12.14	12.64	+ 0.50	..	..	49.4
11-21-16	80.2	123.9	400.2	3122	62.4	8.93	1.58	10.51	12.83	+ 2.32	..	..	50.0
11-22-16	80.2	126.5	400.1	3145	62.2	8.57	1.58	10.15	12.83	+ 2.68	..	..	50.5
11-23-16	81.4	124.9	399.9	3136	61.6	7.84	1.58	9.42	13.02	+ 3.60	4,000,000	74	50.9
11-24-16	81.2	125.1	401.7	3143	61.7	7.76	1.58	9.34	12.99	+ 3.65	..	..	50.9
11-25-16	80.2	125.2	400.6	3135	61.4	5.60	1.58	7.18	12.83	+ 5.65	..	..	51.0
11-26-16	80.5	125.7	401.8	3146	61.2	5.94	1.82	7.76	12.88	+ 5.12	..	..	51.4
11-27-16	80.2	125.0	402.1	3141	60.7	6.03	1.82	7.85	12.83	+ 4.98	4,176,000	70	51.7
11-28-16	80.5	125.5	401.1	3142	60.3	5.06	1.82	6.88	12.88	+ 6.04	..	..	52.1
11-29-16	80.6	124.9	400.7	3135	59.9	4.84	1.82	6.66	12.89	+ 6.23	..	..	52.3
11-30-16	80.2	125.0	402.1	3141	59.6	4.08	2.51	6.59	12.83	+ 6.24	..	..	52.7
12- 1-16	79.8	125.1	400.0	3130	59.3	3.74	2.51	6.25	12.76	+ 6.51	..	..	52.7
12- 2-16	80.4	125.8	400.9	3144	59.2	2.98	2.38	5.36	12.86	+ 7.50	..	..	53.1
12- 3-16	80.2	125.2	400.6	3135	58.4	4.50	2.37	6.87	12.83	+ 5.96	..	..	53.6
12- 4-16	80.6	125.0	400.8	3136	58.5	4.51	2.37	6.88	12.89	+ 6.01	4,563,000	73	53.6
12- 5-16	80.2	124.9	411.2	3136	58.1	5.10	2.37	7.47	12.83	+ 5.36	..	..	53.9
12- 6-16	89.2	103.3	251.5	2358	43.8	5.22	2.61	7.83	14.27	+ 6.44	..	..	53.8
12- 7-16	80.1	124.9	400.3	3131	59.2	7.08	2.61	9.69	12.81	+ 3.12	..	..	52.8
12- 8-16	80.3	125.6	400.6	3139	58.4	6.04	2.61	8.65	12.84	+ 4.19	4,600,000	68	53.7
12- 9-16	80.1	125.4	400.8	3137	57.7	4.47	2.61	7.08	12.81	+ 5.73	..	..	54.3
12-10-16	80.2	125.2	400.6	3135	58.2	5.28	2.80	8.08	12.83	+ 4.75	..	..	53.8
12-11-16	80.7	125.5	400.7	3141	57.4	5.54	2.80	8.34	12.91	+ 4.57	..	..	54.7
12-12-16	80.2	125.6	400.1	3137	57.2	5.05	2.80	7.85	12.83	+ 4.98	4,160,000	73	54.8
12-13-16	91.3	95.4	274.1	2385	43.3	6.00	2.80	8.80	14.60	+ 5.80	..	..	55.0
12-14-16	80.6	125.0	400.2	3134	57.6	4.94	2.80	7.74	12.89	+ 5.15	..	..	54.4
12-15-16	80.0	125.4	400.4	3136	57.0	6.21	2.80	9.01	12.80	+ 3.79	..	..	55.0
12-16-16	145.9	135.1	273.4	2975	54.0	7.19	2.80	9.99	23.34	+13.35	..	..	55.0
12-17-16	80.0	125.8	400.0	3138	57.7	9.00	2.80	11.80	12.80	+ 1.00	..	..	54.3
12-18-16	80.3	125.5	400.4	3138	57.2	7.13	3.03	10.16	12.84	+ 2.68	..	..	54.8
12-19-16	80.0	125.5	400.0	3135	56.5	6.93	3.03	9.96	12.80	+ 2.84	..	..	55.4
12-20-16	80.1	124.9	400.3	3131	56.3	6.49	3.03	9.52	12.81	+ 3.29	..	..	55.6
12-21-16	80.0	125.8	400.0	3138	55.9	5.43	3.03	8.46	12.80	+ 4.34	4,040,000	77	56.1

TABLE 4.—RESULTS OF FORCED FEEDING IN (S. F., MEDICAL NO. 37840) A CASE OF CHRONIC MYELOGENOUS LEUKEMIA, COMPLICATED BY SECONDARY ANEMIA. BROUGHT ABOUT BY HEMORRHAGES FOLLOWING RADIUM THERAPY

Date	Food				Nitrogen per day, gm.					Blood		Weight kg.	
	Protein, gm.	Fat, gm.	Carbo- hydrate, gm.	Total calories	Calories per kilo per day	Urine	Feces	Total output	Intake	Balance	Red blood cells per c. mm.		Hemoglobin per cent
3- 3-17	118.1	165.8	372.8	3554	59.6	.....	3.23	.....	18.89	.....	912,000	20	59.6
3- 4-17	120.5	159.7	319.4	3289	55.1	12.17	3.23	15.40	19.28	+ 3.88	1,152,000	22	.....
3- 5-17	134.9	176.1	375.2	3729	62.5	13.12	3.23	16.35	21.58	+ 5.23	1,536,000	24	.....
3- 6-17	114.6	160.6	399.1	3599	60.3	14.10	3.23	17.33	18.33	+ 1.00	.....	.....	.....
3- 7-17	123.1	159.1	389.1	3580	60.0	10.29	3.23	13.52	19.69	+ 6.17	1,392,000	25	.....
3- 8-17	125.2	155.3	402.4	3607	60.5	13.32	3.23	16.55	20.63	+ 3.48	1,172,000	23	.....
3- 9-17	135.2	184.2	414.0	3964	59.9	10.11	1.97	12.08	21.63	+ 9.55	1,444,000	25	66.1
3-10-17	157.5	174.9	411.6	3961	59.9	13.79	1.97	15.76	25.20	+ 9.44	1,842,000	28	.....
3-11-17	85.7	96.4	298.2	2471	37.3	11.10	1.97	13.07	13.71	+ 0.64	1,572,000	28	.....
3-12-17	137.4	181.3	427.6	4002	.....	9.80	1.97	11.77	21.98	+10.21	1,664,000	30	.....
3-13-17	143.5	176.6	431.7	4001	62.7	11.90	1.97	13.87	22.96	+ 9.09	1,584,000	31	63.7
3-14-17	140.2	174.0	440.9	4001	61.9	13.62	2.46	16.08	22.43	+ 6.35	1,688,000	30	64.6
3-15-17	130.9	189.0	416.6	4002	61.9	9.73	2.46	12.19	20.94	+ 8.75	1,840,000	34	64.6
3-16-17	125.5	172.5	459.7	4004	62.0	10.50	2.46	12.96	20.08	+ 7.12	.....	.....	64.5
3-17-17	156.7	208.0	469.8	4503	69.3	4.39	2.46	7.05	25.07	+18.02	1,836,000	.....	64.9
3-18-17	151.7	189.8	515.5	4501	68.6	12.27	2.46	14.73	24.27	+ 9.54	1,780,000	.....	65.6
3-19-17	145.0	195.0	510.6	4502	68.6	11.28	2.46	13.74	23.20	+ 9.46	.....	.....	65.6
3-20-17	150.8	194.8	505.0	4501	68.4	11.94	2.25	14.19	24.12	+ 9.93	1,984,000	.....	65.8
3-21-17	163.0	206.8	465.6	4500	68.2	12.64	2.25	14.89	20.08	+11.19	1,904,000	.....	66.0
3-22-17	162.3	194.0	514.4	4579	69.0	12.47	2.25	14.72	25.96	+11.24	2,128,000	.....	66.3
3-23-17	154.3	212.7	461.3	4502	67.5	11.38	2.25	13.63	24.68	+11.05	.....	.....	66.6
3-24-17	162.8	214.8	447.6	4500	67.3	12.24	2.25	14.49	26.01	+11.55	1,984,000	38	66.8
3-25-17	147.1	176.9	549.7	4502	67.2	13.20	2.25	15.45	23.33	+ 8.08	2,201,000	38	66.9
3-26-17	165.9	215.4	446.7	4515	67.3	11.71	2.25	13.96	26.54	+12.58	.....	.....	67.0
3-27-17	162.9	211.0	456.5	4502	66.9	13.75	3.17	16.92	26.06	+ 9.14	2,400,000	40	67.2
3-28-17	160.9	201.1	480.8	4501	66.8	14.56	3.17	17.73	25.74	+ 8.01	2,368,000	45	67.3
3-29-17	150.6	217.8	484.4	4629	68.1	14.44	3.17	17.61	24.00	+ 6.48	2,468,000	48	67.9
3-30-17	157.6	208.8	465.8	4498	66.3	12.96	3.17	16.13	25.21	+ 9.08	2,356,000	48	67.8
3-31-17	175.6	179.4	515.5	4502	66.0	15.31	1.59	16.90	28.00	+11.19	2,516,000	51	68.2
4- 1-17	161.5	201.9	478.4	4501	65.8	15.48	1.59	17.07	25.84	+ 8.77	2,892,000	52	68.4
4- 2-17	177.3	180.4	518.0	4528	66.1	13.45	1.59	15.34	28.36	+12.82	.....	.....	68.6
4- 3-17	90.8	100.8	264.8	2395	34.6	12.13	1.59	13.72	14.52	+ 0.80	2,788,000	55	69.1
4- 4-17	149.0	203.9	484.3	4493	66.2	12.88	1.59	14.47	23.84	+ 9.37	3,056,000	55	67.8

It is extremely hazardous to draw conclusions from such a small number of cases in regard to the effect of the diet on the hemoglobin and red cells. The tendency to remissions which cases of pernicious anemia constantly manifest makes it impossible to say definitely what rôle the diet played in influencing the blood picture. In two of the cases the improvement was not very striking; the hemoglobin rose from 36 to 48 per cent in G. R. B. in 28 days (Tables 1 and 5); during that time the patient received two transfusions; in W. B. the hemoglobin and red blood cells were only very slightly increased at the end of 36 days (Tables 3 and 5); in H. M., on the other hand, there was a very marked improvement, the hemoglobin rising from 25 to 60 per cent in 32 days and the red blood cells increasing correspondingly (Tables 2 and 5).

There is no doubt that the nitrogen in these cases is retained. The question as to what use the body makes of it

*Conclusions.*—By means of a forced diet a positive nitrogen balance may be readily obtained in pernicious anemia. Of the three cases observed, there was an improvement in the blood picture in each instance. The latter result must be regarded as suggestive only, inasmuch as too few patients have been studied to warrant a definite general conclusion.

Acknowledgment is due to Miss Susie McFarlane for organizing the Metabolism Ward in which these patients were studied, and for carrying out these difficult feeding experiments in a most efficient manner.

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TABLE 5.—SUMMARY OF RESULTS (TABLES 1, 2, 3 AND 4) OF FORCED FEEDING IN THREE CASES OF PERNICIOUS AND ONE OF SECONDARY ANEMIA

Patient	Period, days	Food per day					Nitrogen per day, gm.			Hemoglobin during period of observation.		Red blood cells, during period of observation	
		Protein, gm.	Fat, gm.	Carbohydrate, gm.	Total calories	Calories per kilo per day	Intake	Output (Urine and Feces)	Balance	First	Last	First	Last
G. R. B.,* Pernicious Anæmia.	28	105	161	395	3547	50.5	16.8*	13.4	+3.4	36	48*	2,016,000	2,760,000*
H. M., Pernicious Anæmia.	32	125	234	344	4099	61.0	20.0	16.6	+3.4	25	60	1,000,000	3,728,000
W. B., Pernicious Anæmia.	36	83	124	371	3015	60.7	13.3	6.5	+6.8	70	77	3,500,000	4,040,000
S. F., Secondary Anæmia.	33	144	183	442	4105	68.9	23.0	14.3	+8.7	20	55	912,000	3,056,000

\* This patient received two transfusions during the period of observation. The nitrogen contained in the transfused blood is not included in the intake; therefore, the nitrogen balance is more favorable in this case than appears in the table; the increase in the Hb. and the R. B. C. must be considered to be due to the transfusions as well as to forced diet.

is another matter. Is it permanently assimilated or would it be excreted if the observations were continued long enough? Is it useful to the body in regenerating blood cells? What proportions of carbohydrate fat and protein will yield the best results? These and a host of other queries are naturally suggested by the cases reported above and it is obvious that the answers must be brought by more extensive experiments.

A control case of secondary anemia (Tables 4 and 5) was treated in the same manner as the patients with pernicious anemia, with the exception that no hydrochloric acid was given. This individual received a higher caloric diet than the other cases. His desire for food was enormous and even with an intake of 68.9 calories per kilo, he claimed that he could easily manage a little more. The nitrogen assimilation in this patient was decidedly higher than in those with pernicious anemia. This may have been accidental, but it suggests that the element of protein destruction does play a considerable rôle in pernicious anemia. The gain in hemoglobin and red blood cells was almost identical with that seen in H. M. (Tables 2 and 5).

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# THE CLINICAL SIGNIFICANCE OF THE IRREGULAR DISTRIBUTION OF VARIOUS CELLS AND PARASITES IN THE BLOOD STREAM AND THE PRODUCTION OF ABORTIVE LEUKÆMIC CHANGES AND OF SPLENOMEGALY IN THE MACACUS RHEBUS

By ANDREW WATSON SELLARDS and WALTER ALBERT BAETJER

## OUTLINE

- I. Predominance of Biological Rather than Mechanical Laws in the Circulation of Various Substances in the Blood Stream.
  1. Consideration of normal substances under normal and under pathologic conditions.
  2. Behavior of foreign material.
    - a. Disappearance of foreign material from the peripheral circulation shortly after injection.
    - b. Temporary disappearance of leucocytes from the circulation after the injection of foreign substances.
    - c. Irregular distribution of parasites in spontaneous infections.
- II. Interpretation of Leucocyte Counts.
  1. Distinction between changes in absolute number and changes in distribution in the body.
    - a. Occurrence of acute temporary leucocytosis.
    - b. Occurrence of acute temporary leucopenia.
  2. Factors governing the leucocyte count.
    - a. Infecting organism.
    - b. Location of infection in host.
    - c. Severity and stage of infection.
- III. Choice of Site of Infection for the Transmission of Infectious Diseases.
  1. Disadvantages of intravenous injection.
    - a. Dilution of material.
    - b. Deleterious action of blood serum and cells.
    - c. Removal of microscopic particles by lungs and other organs.
    - d. Danger of embolism.
  2. Advisability of concentrating the infecting agent in a susceptible area.
- IV. Special Considerations in Regard to Leukæmia.
  1. Selection of spleen as site of injection.
  2. Susceptibility and resistance of spleen to infection.
  3. Mechanical advantages.
  4. Clinical advantages.
  5. Production of abortive leukæmic changes in *Macacus rhesus*.

## PART I. GENERAL CONSIDERATIONS.

Of the many remarkable features connected with the blood and its circulation, considerable interest is associated with the conditions governing the distribution in the circulation of the normal elements of the blood under natural conditions and also of foreign elements upon introduction into the blood stream. Even a cursory examination of a few details is sufficient to disclose the fact that organized cells and probably substances in solution do not circulate according to mechanical laws, but that their distribution is governed by biological conditions.

A simple illustration will make this more explicit. When a suspension of nucleated red corpuscles is injected intravenously into a rabbit, these cells disappear from the circulation within a few minutes instead of becoming equally distributed through the blood, as in a mechanical suspension *in vitro*. In this discussion, mechanical laws are contrasted with biological conditions, but without any intention of opening the question of the explanation that is involved. Thus, it is entirely conceivable that the biological conditions may rest, in their ultimate analysis, either upon physical conditions or upon vitalistic phenomena.

There is a considerable amount of data, extending over a long period in the literature, in regard to the distribution of normal and foreign substances in the blood stream; indeed, there are many observations coming often from unexpected sources which supply information on this subject. We have carried out a few simple experiments to confirm some of the essential phenomena which have been reported. The general clinical significance of these will be discussed briefly, but special attention will be given to the factors bearing upon the transmission of infectious diseases.

## CIRCULATION OF THE NORMAL CONSTITUENTS OF THE BODY

Even under normal conditions, the cellular elements of the blood are not distributed in a purely mechanical way, but are subject to variation as the result of changes which are purely physiological in their nature. Examples of this are to be found in the fluctuations in the number of leucocytes in the peripheral blood, such as the leucocytosis of digestion, after cold baths, and after exercise. Here it is evident that the increase is due essentially not to the withdrawal of fluid from the blood, but to an increase in the number of white cells in the peripheral circulation. The red cell count is also subject to fluctuation. Lamson<sup>1</sup> has shown that there is a mechanism for regulating the red cell content of the circulating blood, that this mechanism is under nervous control and that it is the liver which supplies the body with preformed red cells to meet the acute demands.

There are many types of cells which are ordinarily retained completely in the bone marrow and other blood spaces of the body, but after a more or less severe stimulus these cells appear in the peripheral circulation. Thus it is a little difficult to understand why nucleated red cells are not normally abundant in the circulating blood or why a myelocytæmia develops only after a very considerable stimulus such as the severe infections of diphtheria.

## CIRCULATION OF FOREIGN SUBSTANCES IN THE BLOOD

A series of interesting changes follows the injection of foreign material into the blood stream. Various substances\* either in solution or in suspension, when injected intravenously produce in a few minutes a profound leucopœnia, the majority of the polymorphonuclear cells disappearing from the peripheral circulation and collecting in the blood vessels of the viscera, especially in the lungs and liver, and to a much smaller extent, in the spleen. Moreover, when material in suspension is injected, the foreign particles are also withdrawn promptly from the circulation and collected in the viscera, especially in the lungs, the liver, and to a less extent in the spleen. It is noteworthy that the leucocytes disappear simultaneously with the foreign material and collect in these same viscera. As a general rule, the leucocytes themselves are not destroyed, but after a comparatively short time—a few minutes to a few hours—they return, often in increased numbers, to the peripheral circulation.

This distribution of foreign suspensions was thoroughly studied by Werigo<sup>2</sup>; he found that bacteria and also chemically inert particles such as carmine are promptly removed from the circulating blood. The essentials of these observations have been confirmed by Ewing.<sup>3</sup> Bruce<sup>4</sup>, in 1894, investigated the well known phenomenon of the more or less complete disappearance of the polymorphonuclear cells from the peripheral circulation after the intravenous injection of peptone; *e. g.*, 20 c. c. of a 10 per cent solution. It had been supposed that this sudden disappearance of the white cells was due to a cytolytic action of the peptone, but Bruce was able to show definitely that the leucocytes collected in the blood vessels of the viscera, principally in the lungs, but also in the spleen, and in smaller numbers in the liver. The number appearing in the other organs, however, was almost nil, though the work of some authors indicates that the bone marrow is of some importance.<sup>†</sup> This similarity in the effect of peptone and foreign suspensions upon the distribution of the leucocytes suggests at once the possibility that the peptone may be withdrawn from the circulation corresponding in its behavior to that of suspended particles. Indeed it would be very helpful if the behavior of the leucocytes following the injections of a solution could be used as a criterion to determine whether the foreign substance in solution was distributed equally throughout the circulation, or whether it became concentrated in the viscera in a manner analogous to the behavior of foreign cells.

\* The earliest studies began in 1872, observations being made upon the effect of such substances as curare, fibrin ferment, hæmoglobin, septic fluids, lymph cells, split proteins, chemicals such as uric acid and the urates, and inert substances such as carmine. For detailed references see Sherrington, *Proc. Roy. Soc., Lond.*, 1894, LV, 195.

† Although there is some variation in the individual instances, yet the reports of the various authors indicate that the liver plays a distinctly more prominent part than the spleen in the retention of leucocytes and foreign substances, while the lungs play a more important part than the liver, presumably because material injected intravenously passes first through the lungs.

*Experiments with Bacteria and Red Blood Cells.*—The possibilities of the full significance of these experiments and their bearing upon inoculation experiments in lower animals can be understood best by observing the course of events that follows the intravenous injection of bacteria. The following observations were made in the course of the immunization of a rabbit against a staphylococcus of very low virulence. Upon the third injection, the 24-hour growth from 10 agar slants was emulsified in 3 c. c. of salt solution and injected into a vein of the right ear. A blood smear was made immediately before injection. The time required for injection was about two minutes; when it was completed, a blood smear was made from the left ear immediately and at successive intervals of 5, 10, 20, 30, 40, and 60 minutes. The smear before injection showed an abundance of leucocytes in every field with 88 per cent of polymorphonuclear cells. The smears immediately after injection showed very few white cells. In the smear five minutes after injection the majority of the fields under a 1/12 oil immersion lens were free from white cells. The differential count of 100 cells showed 96 per cent of mononuclear forms. The smear 10 minutes after injection showed increasing numbers of white cells over the preceding one; this increase went on rapidly and a smear 30 minutes after the injection did not differ in its general appearance from the one just before injection. No counts were made of the total number of white cells. The red cells were apparently unaffected. The behavior of the bacteria is even more interesting. With this massive quantity one would expect that they could be seen in the smears. However, the smear made immediately after injection showed no bacteria, either free in the blood or in the few leucocytes that were present; but, in the smears in which the leucocytes were returning to the peripheral blood, staphylococci were frequently found in the polymorphonuclear leucocytes; some cells even contained too many bacteria to be counted readily.

It happened that this animal had already received immunizing doses of staphylococci; on repetition with a normal animal essentially the same features were obtained, though not as sharply; after considerable search only a few bacteria were seen in the leucocytes upon their return to the peripheral circulation. It was found, too, that such large doses often killed the animals suddenly during the course of the injection. Apparently no observations have been conducted to determine whether immunization or infection of an animal would definitely modify its behavior in comparison with that of a normal individual. Any difference in a normal and immune animal in regard to the effect of foreign injections upon the distribution of the leucocytes would be very interesting, inasmuch as it would furnish a reaction for immunity which would be independent of any examination for immune bodies. Bull<sup>5</sup> has recently studied very thoroughly the phenomena of agglutination *in vitro* and *in vivo*. In many instances avirulent organisms are agglutinated *in vivo* in animals whose sera possess no agglutinating action *in vitro*. In contrast to these non-virulent organisms, Bull has made the further very interesting observation that certain virulent organisms are not agglutinated *in vivo* by animals whose serum possesses no agglutinating power *in vitro*. In some

respects it would be difficult to distinguish agglutination *in vivo* from the phenomenon observed in normal animals of the concentration of foreign particles in the viscera.

Hopkins and Parker<sup>8</sup> have very recently noted that after intravenous injection streptococci are quickly withdrawn by the lungs, liver, spleen, and in small numbers by other tissues. These authors have contributed the following very significant observations. Some hours after injection streptococci, which cannot maintain themselves in the circulation of a normal animal, begin to appear in the blood stream. This occurs notwithstanding the fact that the inoculated animal has not lost its power of removing freshly injected organisms.

On injecting typhoid bacilli, an organism ordinarily giving rise to leucopœnia in man, we observed the same immediate results in rabbits as with staphylococci. Five agar slants of an old culture of *B. typhosus* were injected intravenously into a rabbit. The smears after injection showed an outspoken diminution in the number of white cells for a period of 20 minutes.

Nucleated red cells upon injection behaved in the same general manner as other foreign agents, though the changes were less sharp. A half-grown rabbit was injected intravenously with 2 c. c. of a 50 per cent suspension of chicken corpuscles which had been washed twice with normal saline after collecting the blood in 1.5 per cent sodium citrate. The nucleated red cells could be seen in the blood smears in moderate numbers for several minutes after the injection. No phagocytosis was seen at any time. The leucocytes of the rabbit also diminished definitely. Counts were made at various intervals of the number of the red and white cells and the number of nucleated red cells with the following results:

TABLE I.—SHOWING THE RED AND WHITE COUNTS AND THE NUMBER OF NUCLEATED REDS AFTER INTRAVENOUS INJECTION OF A RABBIT WITH CHICKEN CORPUSCLES.

Time intervals	Red count	Leucocyte count	Nucleated red count of injected hen corpuscles
.....	4,500,000	5,500	.....
30 min.*	4,800,000	6,000	.....
3 min.	.....	600	42,000
7 min.	4,800,000	1,600	38,000
18 min.	5,100,000	2,900	12,000
42 min.	5,400,000	3,100	4,500
1½ hrs.	5,600,000	3,200	50
2½ hrs.	5,600,000	3,800	0
3½ hrs.	6,000,000	4,400	0
5½ hrs.	5,000,000	5,200	0

\* Injection: 2 c. c. of washed chicken corpuscles.

The injection of mammalian (human) red cells, however, into a rabbit did not produce a leucopœnia. Certainly, therefore, with the injection of red cells from the same species, as in the blood transfusions, one would not expect any immediate and pronounced leucopœnia.

It has been shown by Goldscheider and Jacob<sup>7</sup> that the subcutaneous injection of an emulsion of certain organs such as the spleen and also the thymus and bone marrow, produces an acute, transient, leucopœnia. We also found that the intraperitoneal injection of pigeon corpuscles in a rabbit produced a

definite, though less extreme, leucopœnia; however, this did not reach its most extreme grade till 20 minutes after the injection, and the white cell count did not return to normal till an hour had elapsed.

#### THE INFECTIOUS DISEASES

In considering the inoculation of diseases into animals, considerable interest centers in the natural distribution of parasites in certain spontaneous infections. There is abundant evidence that when the blood stream is infected, the micro-organisms are not distributed equally throughout the blood. Thus, in typhoid fever, it is very probable that the concentration of bacteria is greater in the spleen than in the peripheral blood and that they persist in the spleen after the circulating blood has become sterile. In connection with the comparative freedom of the extremities from rose spots in typhoid fever, it is interesting to note the apparent difficulty of reaching the peripheral parts of the body by injections into the blood stream. The malarial fevers furnish an excellent illustration of the irregular distribution of micro-organisms. In the æstivo-autumnal type, the parasites are concentrated in the spleen and bone marrow and it is only during the youngest stages of the parasite that the infected cells circulate freely in the peripheral blood. Perhaps one of the most striking and most perplexing examples of all is the profound variation in the case of infection with *Filaria nocturna*. This distribution of pathogenic organisms should be borne in mind in attempting the transmission of infectious diseases to lower animals.

*Interpretation of Leucocyte Counts.*—The consideration of the distribution of cells in the circulating blood is of significance in the interpretation of leucocyte counts. As early as 1892 it was suggested by Rieder,<sup>9</sup> and a little later by Schulz,<sup>10</sup> that the ordinary leucocytoses are due, not to an increased production of white cells, but to a redistribution of them, the cells from the blood spaces being called out into the peripheral circulation at the time of an infectious process. Although this view certainly does not apply to all cases, there are many instances in which it is seen that sudden changes occur in the leucocyte count which are due, not to the formation or destruction of cells, but to a redistribution of the cells in the body. Löwit,<sup>11</sup> in 1892, expressed the prediction that a leucopœnia probably preceded the leucocytosis in many infections, in a manner somewhat analogous to these experimental leucopœnias and leucocytoses. This view received prompt confirmation by Sherrington,<sup>12</sup> and others. There are numerous examples of the development of a leucocytosis, under clinical conditions, in a space of time much too short for the production of new cells. In intestinal obstruction there is often a sudden outpouring of adult polymorphonuclear cells, producing a rise in the white count to 30,000 cells, or more, within five or six hours. Furthermore, there is the example, previously mentioned, of the doubling of the leucocyte count in a few hours after a cold bath. Although the exact time required for the multiplication of some of the lowest types of bacterial cells is extremely short, yet it is obvious that the sudden changes in



the number of blood cells are not due to a destruction and formation of corpuscles, but to a redistribution of cells already existing in the body. At the beginning of an acute leucocytosis the polymorphonuclear cells which appear are mature in their morphology and do not have the appearance of being young and freshly formed. Similarly, in the experimental leucopenias there is no reason to assume a sudden destruction of leucocytes; the injected material in most instances is not toxic *in vitro* for leucocytes and there is no evidence in the morphology of the leucocytes of any toxic action *in vivo*.

The preceding data afford ample ground for the conclusion that the leucocyte counts must be considered as indicating only the number of cells at a given time in the peripheral circulation and not as an index of the absolute number in the entire body. Thus, it is not justifiable to conclude, *a priori*, that there is a destruction of leucocytes in typhoid fever. The leucopenia which develops might readily lead to the assumption that there is an extensive destruction of white cells. The observations of Thayer,<sup>22</sup> however, show that a mild physiological stimulus will promptly raise the number of leucocytes at least to the upper limits of normal. As far as the leucocyte count of the peripheral blood in typhoid fever is concerned, it is obvious, on theoretical grounds, that the absolute number of leucocytes in the body may be either diminished, normal, or increased. The determination of the exact condition must be made by means other than the examination of the circulating blood. The evidence bearing on the question is very meager, but, as far as it goes, it would seem at least possible that the absolute diminution of leucocytes in typhoid may be much less than one has ordinarily supposed.

Moreover, the infecting organism is not the sole factor which influences the white cell count. It is well known that the severity of the infection is important. Thus, pyogenic organisms, which ordinarily produce a leucocytosis, may, in hyperacute infections, produce a leucopenia; if one accepts the work of Sherrington this would mean that the initial leucopenia which often occurs very early in the course of a pyogenic infection may persist in the severe cases instead of giving place to a leucocytosis. There is also another factor which requires consideration; Emerson<sup>23</sup> has noted that the same organism may produce different effects, according to the location of the lesion in the body. Thus, in the after effects of typhoid fever, a peripheral lesion such as may occur in the bones is accompanied by a leucocytosis. This also affords an instance in which typhoid infection is not accompanied by any manifest destruction of leucocytes. Tuberculous infections also indicate that the location of the lesion in the body rather than the infecting micro-organism may sometimes be a determining factor in the effect on the leucocyte count. Thus miliary tuberculosis may be accompanied by a leucopenia, whereas tuberculosis of the meninges usually produces a leucocytosis. The examples afforded by tuberculosis, however, are often complicated by the possibility of secondary infection. Apparently there is no crucial experimental demonstration of these clinical observations that the location of the lesion may occasionally be the determining factor in the leucocyte count.

## PART II. SPECIAL CONSIDERATIONS REGARDING THE TRANSMISSION OF INFECTIOUS DISEASES

It would seem that the diseases to which lower animals are naturally susceptible by intravenous, subcutaneous, or intraperitoneal inoculation have already been determined, at least for the more important infections. A further extension of the ability to transmit diseases to relatively insusceptible species would, in most cases, involve either a modification of these simpler methods of inoculation, or special preparation of the new host. There are many arguments which may be advanced against intravenous injection. In the first place, there is necessarily considerable dilution of the infective material with an extremely good opportunity for the operation of any deleterious action which the plasma and cells of the blood may possess. *A priori*, intravenous injection would seem to be ideal in its possibility of reaching all the organs of the body. However, the foreign material is not only collected primarily in the lungs, liver, and spleen, but the phagocytic cells of the blood also collect in these areas. Moreover, the mechanical disadvantages are not inconsiderable, since the material introduced must be reduced to a fine suspension on account of the danger of embolism; even with a fine emulsion, massive injections for the purpose of overwhelming an animal are often inadvisable on account of the danger of immediate death.

In recent years, not a little attention has been given to the concentration of infective agents in locations of special susceptibility just as therapeutic agents are introduced at the principal site of local infections, as in the routine intraspinal treatment of cerebrospinal meningitis, and in the treatment of tabes by Swift and Ellis.<sup>24</sup> It seems logical to introduce the infective agent into the locations which are involved in spontaneous infections, as in the case of the experimental production of anterior poliomyelitis by inoculation into the central nervous system, or the reproduction of tuberculosis and syphilis by inoculation into the testes.

### CHOICE OF THE SPLEEN FOR INOCULATION EXPERIMENTS

An attempt has been made to take advantage of some of these special methods of inoculation in some experiments on the transmission of leukemia to lower animals. For the inoculation of lower animals, the spleen was selected as the site of injection, not only because this organ is involved in leukæmia, but because it frequently harbors various parasites. At the same time it cannot be regarded as a site of especially low resistance in view of the opportunity for the action of the fluids and cells of the blood in its sinuses and also on account of the phagocytic cells characteristic of the spleen itself. Nevertheless, it is a convenient location for concentrating a large amount of infective tissue in preference to the injection of a comparatively few isolated cells into the blood stream. The spleen is easily exposed by a laparotomy done, of course, under ether. In some animals, especially in cats, it was found that large blebs of the injected material, measuring 1 or 2 cm. in diameter, can be produced under the capsule of the spleen. Since these blebs are not rapidly absorbed, their contents would naturally be much better protected from the immediate

action of the blood serum and the leucocytes than they would in the case of intravenous injection. There is also considerable mechanical advantage in making injections directly into the spleen; large pieces of tissue, such as would be altogether unsuitable for intravenous work, can be introduced into this organ. The spleen readily filters out the grosser particles; in a large number of instances we have had no evidences of embolism in the injection into the spleen of coarse suspensions of various tissues.

From a clinical standpoint the spleen of some animals, notably the monkey, is an excellent organ for observation, since its size can be easily determined by palpation, thereby enabling one to detect very readily a splenomegaly. The advantage of this is evident, both in those cases in which a change in the blood picture occurs, and also during any intervals in which the blood picture is normal while the spleen is enlarged.

Direct inoculation into the spleen and other organs has been practised in a variety of conditions. Musgrave and Clegg<sup>18</sup> attempted to produce amoebic hepatitis by direct injection into the liver of cultures of the limax group growing with *B. typhosus*. Mackie<sup>19</sup> inoculated *Leishmania tropica* into the liver and spleen and v. Seht<sup>20</sup> reported the inoculation of leukæmic blood into the spleen of monkeys. All of these injections into the viscera resulted negatively. Patton<sup>21</sup> obtained some positive results by the direct inoculation of *Leishmania donovani* into the liver.

#### INOCULATION EXPERIMENTS IN LEUKÆMIA

Our own work has been confined to the inoculation of material from various types of splenomegalies into several species of animals. For the most part we confined our attention to acute and subacute leukæmias. There is considerable choice in the selection of material for inoculation. In the patients who were studied, we have used blood for inoculation as a routine, and in one instance some enlarged glands. No patients were available in whom the spleen was enlarged in a suitable manner for puncture and aspiration. In one autopsy case, splenic tissue was obtained for injection. In all, five cases of leukemia were studied; from four of these blood was injected into the spleen of cats, monkeys, and rats. There was frequently considerable disturbance of the blood picture during the first two or three weeks after the injection. The most prominent characteristics were a rise in the leucocyte count, the appearance of unusual cells in the circulation, and frequently an increase in the number of platelets with the appearance of many large forms. Injection of normal blood did not produce such changes. The effect of leukæmic blood was not constant, however, and in no case did it produce a picture of leukæmia. In one instance enlarged glands from a case of acute leukæmia were injected but no definite effect was produced. At most the results were never more than suggestive, and consequently a full report of these cases will not be made at present. One case which came to autopsy, however, deserves special consideration.

#### ACUTE LEUKÆMIA

This case was seen through the kindness of Doctors Leopold and Sexton at the Hebrew Hospital. The patient was a man in the thirties, of rather robust constitution. The total course of his disease was of only a few weeks' duration and he came to the hospital in the last few days of his illness. On admission he was semicomatose and presented at this time the typical clinical features of an advanced pernicious anæmia. There was a moderate degree of jaundice. The spleen and liver were not palpable. The blood picture, however, was by no means a simple one.

The red cells were diminished to 1,500,000 per c. mm. and there was a proportional reduction of hæmoglobin. Only a moderate grade of anisocytosis and poikilocytosis was present. Normoblasts and megaloblasts were abundant. The white count was high, varying from 22,000 to 24,000. Of these cells about 2000 were nucleated reds and of the remainder, 60 per cent were polymorphonuclear in type. There were many rather unusual mononuclear cells but only an occasional myelocyte was seen.

There was nothing remarkable about the platelets either in their morphology or numbers.

The case was clearly an unusual one but seemed to conform most nearly to that group of acute leukæmias which tend to go over into a fairly typical pernicious anæmia.

Direct transfusion of blood produced only a very transient benefit, and exitus occurred a few days after admission to the hospital. Five hours after death the spleen was removed; it was only slightly enlarged. Aerobic and anaerobic cultures of small pieces of splenic tissue on ascitic fluid, blood serum, Dorsett's egg medium, blood agar (NNN medium), and milk, remained sterile for a period of three weeks. A coarse emulsion of the spleen in salt solution was injected into some animals. The following is a general summary of the results which were obtained.

A cat inoculated into the spleen died on the sixth day after injection. The spleen of this animal was inoculated intrasplenically into a young adult cat which died on the sixth day after injection. Subinoculations were made intrasplenically into a monkey from the spleen of this cat. Three weeks later the spleen of the monkey had increased to several times its normal size and the blood picture was characteristic of lymphatic leukæmia. The temperature of the animal was high being 104° and 105°F, but this is not very unusual in normal monkeys. Splenic tissue removed at this time failed to produce any change in a second monkey. The blood picture returned rather rapidly to normal, but the spleen remained large for many weeks. This animal died 15 months later. The autopsy revealed no apparent cause of death. The protocols of these experiments are as follows.

A monkey and a cat were injected intrasplenically with the patient's spleen. This material was highly toxic for the monkey, death taking place within two or three minutes after the injection from cardiac failure. The cat recovered from the operation but became somewhat ill in a few days, coma develop-

ing on the sixth day after injection. Blood smears taken when the animal was in complete coma showed a remarkable picture in that the leucocytes were practically absent. The ordinary preparation for leucocyte counting showed no cells in a 0.1 sq. mm. unit. Blood cultures on milk showed a growth of a micrococcus in one of three tubes, indicating a secondary bacterial invasion. This animal was sacrificed just before death and subinoculations were made, spleen, blood, and bone-marrow being used, one cat being employed for each substance. All of the animals remained perfectly well except the one receiving an injection of spleen. This animal died on the sixth day and blood smears made a few hours before death also showed a complete absence of leucocytes. This is open to the interpretation that in the acutely fatal cases some leucotoxin produced extensive destruction of the white cells. A simpler explanation, however, suggests itself, since in some instances control animals injected with large doses of bacteria also showed when in the stage of coma a similar absence of leucocytes. Cultures from the heart blood of this second cat showed prompt growth on milk. The spleen itself showed no gross changes; small portions were emulsified and injected into the spleen of a monkey (*Macacus rhesus*). This cat died after three days from a complicating peritonitis whereas the monkey remained apparently well. The operative incision healed promptly with no evidence of any secondary infection. The white blood counts showed some fluctuation, but no significance could be attached to them. The count fell at first from a normal of 27,000 to 13,000. During the next three weeks it rose gradually to 56,000, a significant change occurring in the differential. In this species of monkey, the mononuclear elements are normally very high as compared with man; a typical count of this individual before injection showed 35 per cent polymorphonuclear cells, and a total of 57 per cent mononuclears with 8 per cent of cells unclassified. During the rise in the white count, however, the polymorphonuclears fell to 19 per cent, and the mononuclears rose to 81 per cent. Taking fully into consideration the normal blood picture of the *Macacus rhesus*, the smear was distinctly characteristic of a leukaemia of the lymphatic type. The evidence of a leukæmic change as contrasted with a leucocytosis was seen, both in the low percentage of polymorphonuclear cells in the blood and in the appearance of some immature cells, such as a few myeloblasts. These cells were not found in the normal blood of this individual before injection and in the examination of 10 other macacus monkeys they occurred only in a few individuals and in very small numbers. This change in the blood picture lasted for several days and then returned to normal. In addition to the change in the blood picture a well marked splenomegaly developed. Three weeks after the injection, the spleen was found to be several times larger than its normal size. On exploration, this increase in size was found to be due, not to swelling and congestion, for the spleen was hard and firm, measuring four times its size before injection. On surgical extirpation of about one-fourth of the organ, it was so firm that relatively little hæmorrhage took place. Histologically there was nothing remarkable.

This splenic tissue obtained by operation was injected into the spleen of a monkey and into a kitten. Cultures were also made on blood agar, on ascitic fluid containing fresh tissue and on Dorsett's egg medium. The animals remained well. During the next three months no significant change occurred either in the blood count or in the size of the spleen. The cultures were observed for three weeks but no growth developed.

Some control observations were made in order to determine as accurately as possible the cause for the enlargement of the spleen and the change in the blood occurring in the monkey. It is important to eliminate the ordinary bacterial causes especially secondary pyogenic infection and tuberculosis.

Apparently a few bacteria were present in the cat's spleen which was injected into the monkey, since the blood of this cat showed growth in milk of a coccus. This is an unfortunate circumstance but secondary infection in a moribund animal readily develops. These organisms apparently were not present in the patient's spleen since the cultures on various media showed no growth. There is considerable evidence that this organism could not have been responsible for the change observed in the monkey. An absolute increase in mononuclear cells is not a characteristic of pyogenic infection; and moreover there was no evidence of any local or general sepsis. Finally a control experiment was done injecting 2 c. c. of a milk culture of this micrococcus into the spleen of a normal monkey. A typical pyogenic leucocytosis resulted. The leucocytes rose in 24 hours from 8000 to 10,000 and the proportion of polymorphonuclear cells rose from 36 to 95 per cent. The blood picture gradually returned to normal and the spleen did not enlarge. Ten months later this animal developed several metastatic abscesses. The spleen did not enlarge and the white count rose to 59,000 with 90 per cent polymorphonuclear cells. He soon recovered from these infections.

If there were any evidence by which the production of the leukæmia picture could be ascribed to the bacteria present, it would be an extremely interesting factor in bringing about the correlation of the leucocytoses with the leukæmias, since the hypothesis has been advanced that the two conditions are part of the same process, and that the same agent, if allowed to act for a long period, may produce first a leucocytosis, and subsequently, with the exhaustion of the bone marrow, a leukæmic picture may develop.

The consideration of tuberculosis is important and fortunately it can be excluded rather readily. In the first place this monkey developing a splenomegaly, lived for many months after this experiment and when death eventually occurred, the autopsy showed no evidence of either active or healed lesions of tuberculosis. Moreover, when the spleen had reached its maximum size, a portion that was excised showed no histological evidence of tuberculosis and no growth developed on appropriate media. A second monkey inoculated with the tissue did not develop tuberculosis.

From the data which have been presented the conclusion naturally follows that the enlargement of the spleen accom-



panied by the leukæmic blood picture could not be attributed to pyogenic infection or to tuberculosis.

This leukæmic change was of short duration and could not be transmitted by subinoculation. Nevertheless it is of interest in view of the many entirely futile attempts to produce either leukæmia or splenomegaly experimentally.

It is perhaps a little difficult to form a distinct impression of the difference in these blood pictures simply from an analysis of the total and the differential counts. Accordingly we have reproduced typical fields from three of the more important preparations: namely, of (1) a normal monkey; (2) the same monkey after injection with material coming originally from a case of leukæmia in man; and (3) the reaction of a monkey to pyogenic bacteria.

#### SUMMARY

I. The circulation of normal and foreign substances in the blood often fails to follow mechanical laws, either under normal or pathologic conditions. An unequal distribution occurs which is governed by biological conditions. The corpuscles of the blood are not distributed with mechanical uniformity throughout the blood channels; parasites invading the blood stream are often concentrated in the blood spaces of the viscera.

II. Upon injection of a variety of substances into the circulation, the injected substance and the leucocytes, especially the polymorphonuclears, disappear from the peripheral circulation within a few minutes and collect in the blood vessels of the viscera principally in the lungs and liver. Within a short time the leucocytes return to the peripheral circulation, often in increased numbers and sometimes after having phagocytized the injected material.

III. The leucocyte count cannot be interpreted as an index of absolute change in number of leucocytes in the entire body, for it often indicates only changes in distribution rather than a formation or destruction of white cells. Thus, the total white count does not constitute crucial evidence that there is an absolute leucopenia in typhoid fever. There are at least three factors governing the leucocyte count; namely, (1) the infecting organism; (2) the severity of the infection; and (3) the location of the infection in the host.

IV. The failure of foreign substances to be distributed in the blood stream according to mechanical laws has an important bearing on the transmission of infectious diseases. It offers many arguments against intravenous injections of infective material for the transmission of a disease to resistant animals for the reason that,

1. Considerable dilution of the material necessarily occurs.
2. Extensive opportunity is offered for the action of any deleterious effects which the fluids and cells of the blood may exert.
3. Fine suspensions and limited amounts of material are necessary in order to avoid embolism and sudden death.

4. Finely suspended matter is not distributed equally throughout the blood stream, but a large proportion is removed by the lungs.

Many of these objections could, of course, be overcome by an intra-arterial injection if it were made into the proper side of the circulation.

V. Inoculation into the spleen for the transmission of splenomegalies to lower animals possesses certain advantages:

1. It avoids many of the disadvantages of intravenous injection.
2. The injected material can be temporarily protected from the immediate action of the fluids and cells of the body.
3. The mechanical advantage is considerable, since large pieces of material can be used.
4. The spleen is well adapted for study, since changes in its size in certain animals can be readily determined by palpation.

VI. Inoculation of the spleen of a case of acute leukæmia into the spleens of cats produced death acutely. Inoculation from these cats into a spleen of a monkey produced a chronic splenomegaly with an acute temporary leukæmic change in the blood picture. The production of even abortive leukæmic changes and of splenomegaly in a normal animal by inoculation of human material is of interest.

This work was conducted during 1914 in the clinic of Prof. Lewellys F. Barker at the Johns Hopkins Hospital. A report was made at that time before the Johns Hopkins Medical Society. In the meantime the continuance of these studies has been seriously interrupted and has finally been suspended for the time being. Consequently, it has seemed advisable to make this incomplete report without waiting for confirmation and extension of these results. It is a pleasure to thank Dr. Barker for a helpful and stimulating interest.

#### DESCRIPTION OF ILLUSTRATIONS

##### ROMANOWSKY STAIN (WILSON'S)

- FIG. 1. Typical field from blood smear of normal monkey.
- FIG. 2. The same monkey three weeks after inoculation with splenic tissue from an animal injected with the spleen from a case of leukæmia in man.
- FIG. 3. Control monkey inoculated with pyogenic organisms to show the effect on the blood picture.

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## MEMORIAL MEETING TO DR. THEODORE CALDWELL JANEWAY

A memorial meeting for Dr. Theodore C. Janeway, late Professor of Medicine to The Johns Hopkins University and Physician-in-Chief to the Hospital, was held in the hall of the Engineering Building of the university at Homewood, on Sunday afternoon, March 10. The meeting was opened with prayer by Rev. Dr. Arthur B. Kinsolving, and addresses were made by President Frank J. Goodnow, Johns Hopkins University; Mr. B. Preston Clark, Boston, Mass.; Dr. John Howland, Johns Hopkins University; Dr. Alexander Lambert, Dean of the Medical School of Columbia University; Dr. David Edsall, Harvard University; Major General William C. Gorgas, Surgeon General, U. S. Army, and Dr. William H. Welch, Johns Hopkins University.

**Rev. Dr. Arthur B. Kinsolving.**—O God our Father, from whom we come, to whom we go, in whose gracious protection Thy children abide in whatsoever place and condition they may be; we thank Thee for all the goodly company of those who have helped us by their eminent labors and noble examples.

We yield unto Thee high praise and hearty thanks for the graces and virtues of him we are met to memorialize, for the beneficent skill of the good physician, for the diligent man of science and research, for the fearless follower of truth, for the strong and inspiring friend, for the devout Christian who amid his thronging duties made room in his life for God, for the citizen who withheld not his life at his country's call.

Help us each to grow stronger, more gentle, brave and true by calling to remembrance his gifts of thought and speech, his quick and understanding sympathy, his vision of service, and duty. Grant that all that he was here may be ripened and expanded there, and that he may find employment in the spacious fields of eternity.

Help us all, O God, to rejoice more and more in other men's strength and brightness and success, and set our hearts free to serve Thee better, and more perfectly to love Thee,

Through Jesus Christ our Saviour.

**President Frank J. Goodnow.**—We have come together this afternoon to honor the memory of Theodore Caldwell Janeway whose death in the service of his country has caused such a vacancy in our ranks.

Prior to the breaking out of the war, to the prosecution of which Dr. Janeway gave so much of his time and strength, he had won an enviable reputation as practitioner, teacher, organizer and student. His love for the scientific side of his profession was so great that when the opportunity presented itself he gave up active practice to devote his entire time to teaching and investigation. At the time this country entered

as a participant in the great conflict now raging, he had succeeded in putting his department in the Hospital and Medical School in a state of rare efficiency.

The call of his country could not, however, be denied. The extra duties which he then assumed were a great addition to already burdensome responsibilities. His regretted death cut him off at the height of his usefulness. It leaves us, his friends, however, with the consolation that the standards he set will live long after he has gone out of our lives. We mourn the loss of a kindly presence. We cherish the memory of a sincere personality, a strong character, an able man.

**Mr. B. Preston Clark.**—It is entirely natural that we who know and love Theodore Janeway should each know best some special side of that nature, which touched life so profoundly, and from so many angles.

Though he and I have known each other for less than ten years, it seems as though we had always known each other.

My first meeting with him was after a remarkable diagnosis. The patient, one of my own boys, was recovering from a serious illness. I tried to express my gratitude as best I could, and in that quick way of his he said "Most of the agencies that make for human health and disease are microscopic in their character, and we really know very little about any of them." That attitude of simple humility toward the profession of which he was a master I can never forget.

I have not the knowledge, as so many here to day have, to gauge in any broad way his professional skill, I being only a layman, a business man. I only know that it must have been wonderful. It has been on other sides that I have known him.

When some difficult and intricate industrial problem has been under consideration, I have taken the opportunity when it was possible to discuss it with him. And we never had such a discussion without my learning much from his method of approach which helped to clarify the issue and to assist in finding a solution. For his mind had a universal quality.

Of just one other quality of his vivid personality I shall speak and only one. And that is his apprehension of the invisible and the spiritual as being more truly real than aught which we can touch or handle. That is to me the crown of his personality and its very essence.

During this last summer on his short vacation we lost no moment when we could be together, and the same was true on my own hurried trips to Washington during the early winter. And always I was conscious in him of a great and increasing power of leadership.

Leadership is a subtle and elusive thing, not to be limited or exactly defined. But of one thing we can be sure. The



Theodore D. Sherris.





great leader cares so deeply for his cause; he sees his vision so clearly, that he forgets himself. He sacrifices himself without knowing that he is doing so; he sees in sacrifice simply boundless opportunity. He draws men after him; because they follow, not him alone. They follow that which he follows. As in the battles of old the fighters followed the gigantic shadowy warrior who led them to victory.

And when in battle a leader, a true leader, falls, the charge checks for perhaps a brief moment, but it goes forward with undiminished power, and the charge is driven home.

Such a vision of the invisible and the eternal was given to Theodore Janeway; such a leader he was and is; and may it be given to us in the light of that vision to follow that which he followed; to raise aloft the standard which has fallen from his hand; to see in sacrifice simply opportunity; to live worthily of the vision, to close up the ranks, and to carry the charge home. Thus shall we pay a living tribute to a great leader, and a yet greater man.

**Dr. John Howland.**—For many years I have known and admired Theodore Janeway. We were boys together at school, we were at college and in the medical school at the same time, we were contemporaries in New York and, finally, were colleagues in Baltimore together. I may speak of him, then, in many stages of his career, for I saw him grow from a school-boy into a man and finally become a leader of medicine.

On looking back, it is easy to see that he exhibited strikingly as a boy the qualities that made him distinguished as a man. There was nothing that he had to put behind him or forget or outgrow, nor was there an abrupt change from the irresponsibilities of youth to the duties of later life. It was just a gradual, even growth and development in a life of singular rectitude.

He was, in school and college, conscientious, persevering and serious. He matured early. He was studious and always a hard worker but there was nothing of the book-worm about him. He was merry and keen in regard to all the activities of school and college life. Cheerful and well liked by all, he gave the gift of his intimacy to but few.

Thus, Janeway went through college, leaving behind an enviable reputation in those courses that prepare for a medical career, for he early knew what his profession was to be, and, alive to the responsibility of one who bears a distinguished name and also because he believed in doing all important things well, he worked with characteristic diligence and enthusiasm. Those who taught him could outline his future.

It was, however, in his medical school course that he really shone. He was the first or second man in a singularly good class and, by virtue of this fact, became eligible to compete for a number of prizes of very considerable money value. Then he did a characteristic thing, the reason for which was only surmised and of which he never spoke to any one. He did not compete for the prizes. It was quite plain that he would have been successful and he must have known it for he judged fairly his own abilities though he never overestimated them. But he knew there were others who needed the reward more

than he. Such consideration for others was not an isolated example. It was a constant and conspicuous trait of a generous spirit, exhibited throughout his whole life.

He served through his hospital years with great credit and then began the practice of medicine with his father. It is seldom that any one is fortunate enough to work under such inspiration and guidance. Dr. Janeway, the elder, was a medical man in a generation. He had intuition, great knowledge, his experience was enormous and his judgment unerring. Between him and his son there was complete community of spirit and entire intellectual sympathy.

It is one of the regrettable things in medicine that a master of diagnosis cannot transmit his experience to succeeding generations. His knowledge he may, in books and pamphlets; his experience usually dies with him unless the opportunity is given to the pupil, by close and constant association, to see repeatedly the attitude of mind toward medical problems and thus to absorb some of the mental processes of the master. This opportunity was given to Theodore Janeway and was eagerly utilized. The years that they were together must have been a period of intense enjoyment and a wonderful experience for both father and son. They were absorbed day after day in entire accord upon the work that interested them most.

It was a period of rapid growth for Theodore Janeway, so rapid that it became in a short time evident to all his contemporaries that he was to be a man of prominence and this conviction steadily grew; for it was readily recognized that he was not only a diagnostician of great skill, always sound and often brilliant, but that he was a capable experimenter and an especially gifted teacher.

He began to teach first in a minor capacity at The University and Bellevue Medical College and later he advanced to more important positions until he finally was called to the Bard Professorship of Medicine at the College of Physicians and Surgeons.

To all forms of teaching he added something new, something that made the subject more interesting, more stimulating. In the teaching of physical diagnosis, he introduced simple mechanical experiments to demonstrate the principles of physics underlying the signs. He was the first in New York City to teach medicine from the standpoint that disease is a deviation from the normal physiological basis and he, together with Oertel, introduced, at the City Hospital, the clinical-pathological conference, a form of exercise that has been widely adopted. And it should not be forgotten that in this country the clinical study of the blood pressure began with him and that he devised the first instrument that made the study of this possible for us at the bedside.

Janeway, at one time or another, was connected with a number of different dispensaries and hospitals. Many of the services he reorganized and all were improved by better methods, greater service and more complete cooperation. When he went to the City Hospital on Blackwell's Island, the service was neglected, the internes were poor in ability and hard to obtain. In a short time, everything was changed so that it

was an active, most effective organization with men eagerly striving for positions upon his staff.

Occupied as he was with teaching, research, hospital work and practice, he, nevertheless, found time to give advice and assistance to the charitable organizations that try to improve the conditions of those incapacitated for work by accident and disease. He appreciated the distress that frequently accompanies disease and he felt that he could and would contribute to an intelligent amelioration of this. For many years he was closely identified with the Association for Improving the Condition of the Poor.

In all his work, indeed in all his life, he was as conscientious as a man could be. He was thoughtful of others, he made the way easier for many but he would not spare himself. He worked incessantly and constantly beyond his physical capacity. He could not be persuaded to do less. It was part of his creed that if things were to be done, they were to be done well no matter at what cost to himself. He was mentally sound and he was ruggedly honest with all and especially with himself. He practiced medicine and he taught medicine honestly. If there were an error in diagnosis, he was always the first to acknowledge it; he would claim no part in any work that was not his own, and he could teach medicine only upon the basis of established fact. To those who knew him, he was a loyal and devoted friend, a companion full of humor but also of inspiration. And so I felt and shall always feel that when Theodore Janeway died, at the height of his ability and usefulness, medicine suffered a grievous loss and a splendid man was gathered to his fathers.

**Dr. Alexander Lambert.**—In New York we of the medical profession have never ceased to look upon Theodore C. Janeway as one of us and to regard him as a New Yorker. Outside of the profession the city still asks for him for advice although he has been away from his inherited professional haunts for nearly four years. New York has never been without a Doctor Janeway for more than fifty years and that city, in spite of its two hundred new citizens each day, is a city of habit and tradition especially in medical affairs. A consultation with Doctor Janeway was a habit so ingrained that it is not yet quite broken, at least in the thought and subconscious longing of the population. This habit was founded by Theodore Janeway's father who won the position of first consultant in New York by giving a careful study to each problem presented to him before drawing upon his remarkable experience in the pathological amphitheater and the clinical wards of the three great hospitals which he had served.

New York medicine, to a superficial view, often seems tainted with commercial methods, harassed by professional competition and hampered in development because its successful practitioners of the medical art are broad catholic citizens of the world and not intensive scientific investigators. Such a judgment is truly superficial for the influence of New York has been widely spread through the United States by the activity in the teaching hospitals of the city of certain great personalities who stood for an ideal to make the practice

of medicine a humane art applied to human beings by human beings.

Both Janeways, father and son, represented this class in the metropolitan community—Edward G. Janeway exerted his greatest influence in this broad New York way upon many generations of students from all the colleges of the city and from many outside of it as a physician of Bellevue Hospital and not in any narrow field limited by academic walls.

Theodore C. Janeway inherited a remarkable memory which he trained to store up both the facts to be found in medical literature and also the varied clinical pictures that were constantly being brought to his father's office for interpretation. In that office under that chief he developed a great diagnostic insight which however he never allowed to lead him across lots to his goal without first exhausting every known method of physical and laboratory study. He was a hard taskmaster to himself both as a practitioner and as a consultant and left no step unconsidered which would assist his fellow worker and colleague or be of assistance to the sick and ailing patient. Theodore Janeway was trained under the exacting conditions of a large consulting practice in a large city. He nevertheless never became commercial and showed a remarkable aptitude for applying scientific methods to the study of clinical medicine and for stimulating others to pursue a career in the research laboratories connected with his hospital wards. His ability in this field has meant much to New York in general and to the College of Physicians and Surgeons in particular.

It was the special opportunity of the college to call Theodore Janeway to the career of a teacher in a broad field and to raise him at one step from an instructorship of associate grade to the highest position in clinical medicine within the gift of Columbia University, the Bard Professorship of the Practice of Medicine. He succeeded in his task from the outset and became widely known in New York and the whole country as a teacher who could analyze the process of reasoning which led to his diagnosis, who possessed the art of graphic description to an unusual degree and who instilled in his students and in the instructors of his department a rigid thoroughness in routine and an exact precision in thought and expression.

As an executive Theodore Janeway was familiar with every detail of his department. He was always accessible to his colleagues for counsel and eager to consider advice from an assistant as from an equal. He was earnestly devoted to his conception of the right and ready to fight or to make any personal sacrifices for his ideals. He left his mark on New York medicine by taking charge of a department bare of every facility for modern teaching and research and after a short four years he left it equipped with a library, which had been his own, with a hospital service, with research laboratories and with the nucleus of a staff devoted to teaching and to research. Columbia University and New York were that much poorer when he left to assume the work in Baltimore at Johns Hopkins.

There are in New York many younger men in the profession who have impressed on me, since the untimely death of Theodore Janeway, their sense of personal loss and their gratitude to him for an early insight into the high ideals of medicine,



for an appreciation of the necessity for absolute medical honesty and the need for a constant revision of opinion as new facts are discovered and for having labored with a man devoted to a thorough and systematic habit of work.

It was my personal privilege to start Theodore Janeway as a student on his medical career and to be among the first to teach him, to whom I later went to learn. It is my present privilege to add my testimony to his worth as a clinician, to his ability as a teacher, to his loyalty to his friends and to the permanent impress for good which he made on medical education in New York City. His work and character are remembered there as an exponent of all that is good and all that is best in a profession which is still controlled by ideals; a profession which is still advanced by the power of the human brain and hand to do the most perfect work in a world so largely controlled and ruled by the machinery of construction and of destruction.

**Dr. David Edsall.**—In periods of great change in thought and policy and in the nature of individual responsibilities clear vision, high purpose, and a determined idealism tempered by wide judgment, are qualities of such importance as to overbalance others. Doubtless in all times of great activity and change in work of whatever sort these qualities have seemed to be needed as never before. We should not do justice to our forbears in medicine if we exalted too far above theirs the tasks that have fallen upon those to whom we have looked for leadership, but we nevertheless can but believe that in the past two or three decades, the complexities and responsibilities of medicine have been largely added to and there have been in progress and in prospect such fundamental changes, not only in knowledge but in policy, that qualities and training fitting for wise guidance have been especially demanded and more desirable than any others. And in recent times the greater weight of these new responsibilities has fallen upon clinicians, for the non-clinical branches had passed through their most acute travail earlier and had become somewhat adjusted to the changes when the clinician met the need of a new alignment in viewpoint and in manner of life and thought. To the clinician the complexity has been increased by the need of retaining much that his colleagues could cast off and nevertheless of readjusting his methods in much the same manner as they. He has had to add a multiplicity of precise methods to the earlier less exact ones that demanded chiefly training in observation and interpretation, but he has been obliged to retain undiminished his regard for the latter. He has had need to undergo the still more difficult mental adjustment to experimental instead of observational methods of thought and especially of research, as the yield from the older methods became less fruitful; and yet he has had to retain a cautious respect for even purely empirical observations. In academic medicine he has had to make decisions and adjustments similar to those of his colleagues in the distribution of his energies and in manner of life, but he has had to cherish and to train equally the power of human understanding and the patient study of character and the attention

to petty affairs that are so spendthrift of time and energy, but without which he would overlook his main duty, the safeguarding of individual human life and health.

These changes have been of gradual growth but Theodore Janeway passed through the period of most rapid transformation, the period in which alterations have been at times so sudden and radical as to arouse wide differences of opinion, and in which clear judgment and determination have been needed to avoid undue haste and enthusiasm as against complacent inertia.

Long training with his distinguished father and a very lovely veneration of him would of themselves have sufficed to prevent him from being led by enthusiasm for the newer types of study to belittle the value of those methods that made Edward Janeway so eminent. But by temperament as well, Theodore Janeway was conspicuously attached to and he was rarely gifted in the painstaking clinical and pathological observation of disease, and through years of accumulated study of literature of disease in its progress and of its pathological results, he acquired that skill and clarity in the observation and discussion of matters of diagnosis and treatment that left no one his superior as a clinician or as a contributor to directly practical clinical medicine and gave him his exceptional strength as a teacher of practice.

Clinical medicine, especially in its research activities, was coming constantly closer to the laboratory and it was inevitable that this rapprochement should become increasingly intimate. But general sympathy with this essential movement could be secured early and its progress hastened far more through keen appreciation of what was good in the older methods as well as the new than through a partisan championship of the new alone. It was a great and permanent service that Theodore Janeway rendered to medicine in furnishing so fine and timely and so outstanding a demonstration that a man may be a devoted master in the older methods and at the same time an eager student and contributor in the new, and likewise a stimulus and guide equally to those whose pathway leads them chiefly into the one or the other and especially to those who would co-ordinate the two. Nothing has been more needed. No one has done it so well. To have had great opportunity and power to exert influence upon the things that mould the character of one's profession and to have used them so as to have left debtor both radical and conservative is a singularly rare and valuable service. His success in this was in part due to the training and judgment that I have indicated, in part to a very broad fund of knowledge ever at the service of others, but no less than to these it was due to that type of ardent sympathy and idealism that leaves a bit of fire in those it touches. To many who came close to him even occasionally there must stand out as more helpful even than his contributions to knowledge the picture of a nobility of purpose, an abundant sympathy and comprehension, fired by that trace of desire for the unattainable which, when restrained by sanity of judgment, lifts up a leader to reach the attainable and without which even genius secures few disciples; and to those engaged in the study of problems in any branch of medicine there will always remain a keen and grateful memory of the inspiring thought-

fulness with which he constantly kept their work in mind and put at their service as few remember to do anything helpful that came up in his own busy work.

And this catholic sympathy and interest extended beyond his labors for the individual sick and for those who deal with them alone. He comprehended clearly the interdependence of health and of many community problems and of the ways in which the physician may attach himself to social movements and still remain within the fields for which his training fits him. He was one of a very few in medicine to whom those who struggle with these problems turned confidently for wise advice and generous aid and yet he saw clearly the limits as well as the extent of the physician's province in these matters. Peculiarly devoted as he was to the human relations of the practice of medicine, whatever the recompense, it was in very considerable part a great sacrifice to relinquish for purely academic work and increased burdens of administration the grateful intimate personal side of the life of the physician who is chosen by the patient, a loss that he did not cease to feel. But when the choice had to be made it was at once made with sole thought of the way in which he could best meet the needs of medicine. This decision was typical of an attitude of mind that was and will remain a powerful part of his influence upon medicine.

There is a comforting sweetness to those who held him personally very dear in the generous evidence of the breadth and variety of his influence that comes from those in all these varied forms of work that the clinician meets in normal times. Never greatly endowed with vigor he had constantly in civil conditions "ventured life and love and health" ever with the unselfish thought of service. It is but natural that all these should have been ventured again, ventured then, alas, finally, in single-hearted loyalty to his country after having given in this work further distinguished exhibition of skill and judgment in organizing and placing men and in the determination of methods and policies.

To have been a wise and trusted pilot in his high calling, to have helped signally to weld together opposing and disorganizing forces, to have guided clearly juniors and contemporaries not only in deeds but in motives, and to have left a light burning in all the forms of his high endeavor, to have done all these is to have done more potent things than are often done.

A thought that has become commonplace through repetition may still seem new and moving when we recall it as we first met it. When I think of the problem of immortality, I always go back to my boyhood to the time when I heard a cold, repressed, unreligious man, after listening apparently uninterested to a discussion of such matters, say suddenly and with a sternness that still arrests my attention that whatever one feels about a future life, immortality of some degree and kind is inevitable for all of us, that we can not prevent the indefinite perpetuation of our influence for good or evil even though the source of the influence may soon become untraceable and unnamable.

"Not till the hours of light return,  
All we have built do we discern."

If we can visualize the increasing growth of the wave from an impulse as it passes on from group to group we may find recompense for the unaccountable brevity of a high career in the enduring influence of a true and strong force that will still act when other more prolonged energies have become relatively spent and inert.

**Major General William C. Gorgas, Surgeon General, U. S. Army.**—My acquaintance with Dr. Janeway began originally when he was a little child. In the early days of my medical career I was house physician in Bellevue Hospital and in the division over which Dr. Janeway, Sr., Dr. Flint and Dr. Lusk presided, three names to conjure with in the province of medicine.

The elder Dr. Janeway at that time was much interested in the pathological work of his division, and it was my duty there to be associated with him and to assist in his researches. Through my visits to Dr. Janeway's house, I first met the younger Dr. Janeway, as I have said, as a little child. In after life I met him occasionally at the meetings of medical societies and other gatherings of our profession. At that time I knew him only as an eminent professional man.

On the entry of our nation into the present war, it became necessary for my office to find men prominent in civil life, above the average mark in their profession, to assist in the selection of those who were to serve as my staff in building up the large machinery which is necessary in the conservation of the health of the armed forces.

I appealed to Dr. Janeway to take over the direction of an important division in the office, and he, as was so characteristic of him, promptly gave up his work in Baltimore almost entirely and devoted himself heart and soul to the furtherance of the interests of his country here in Washington. He was with me up to the time of his death and organized in a most efficient manner the division of which he was the head.

As the head of the Medical Corps, his death was a keen loss to me, aside from the regret which I feel at the death of a friend whom I trusted and admired.

In all the machinery of a busy office, such as ours in Washington, there is not much time for personal intercourse, but I did see Dr. Janeway many times in consultation over matters concerning the routine of his division.

Less than a month before his death, I had occasion to inspect with him some of the southern camps. Our contact at that time was close and intimately personal, for we lived and travelled together for a considerable length of time. Knowing Dr. Janeway in this way personally, for the first time, I was much drawn to him and attracted by the fineness of his character; by his constant cheery manner; his optimistic outlook in the face of any difficulty. The work during this trip was hard and exacting, the days often mounting up to eight and ten hours of constant work; but in the face of it all, he was ever patient, ever alert and always bright and cheerful. I feel that it was a privilege to know in this inti-

mate way the personal side, as well as to realize, as I have for a long time, the fine qualities of his professional mind.

One of the former speakers has made a remark which appealed to me strongly. He has brought up the question as to whether it is altogether regrettable for a man to die in his prime, at the height of his power and vigor and force. In reading military history, I have often thought that no soldier's death was more fortunate than that of Stonewall Jackson, a man who had risen in two years to a position in his profession probably never excelled by any of his predecessors of the English speaking race. His military career had been eminently successful and was markedly so in the battle in which he gave his life for his cause. It had been a day of unexampled success; he had extricated his chief from an apparently impossible position; at the moment when he was stricken down he was following a routed and defeated army; so far as he could see, his course was successful. What greater or more welcome death could a soldier have than to be called at such a time?

Viewed from this aspect, I cannot think that Dr. Janeway's death is altogether regrettable. He was at the prime of life and at the period of exaltation from personal success. He had made his name honored and admired. Of course, we who are left behind see it differently, for apparently Dr. Janeway had within him more years of useful work for his fellow man, and I, as Surgeon General, cannot but feel the loss which his death means in the work to which I am pledged.

But from the standpoint of the individual, if we had to choose our period of death, would most of us take the time when our faculties have begun to deteriorate, when we are old and past the prime, or would we prefer to finish our career when we are strong and sure and in the full vigor of all accomplishment?

And so, today I stand in a double capacity: as the Surgeon General of the Army, I feel keenly the loss of an almost essential part of my organization. As a man and a friend, I feel that sense of personal loss which is inevitable at the departure of those we love.

**Dr. William H. Welch.**—There is little indeed to add to the tributes which have already been paid to our beloved friend and colleague, Dr. Theodore Janeway. He has been spoken of as the "younger Janeway" and reference has very appropriately been made of his father, who was a great influence in his life. His inheritance, manifested by those remarkable traits of mind and character, was the very best on the paternal and maternal side. His native endowments were high. To those were added an admirable education adapted to his peculiar qualities, and with a view to his profession. He was trained at the Yale Scientific School, and there he followed that course which was in no small part organized and developed by the first president of this university, President Gilman, at the time he was connected with the scientific school at Yale. That was the first course inaugurated which took into consideration the need of specialized training for those who contemplated the study of medicine.

With this inheritance and this training, Dr. Janeway entered upon the study of medicine in New York. He graduated at Columbia University, but his education only then began. It continued through his life.

As I have said the greatest influence was that of his father. Like General Gorgas I also had the privilege of coming under the inspiration of the elder Janeway, who was surely one of the most remarkable men in our profession in our generation, indeed in the medical history of our country. A man whom future generations I think can hardly estimate as we who knew him estimated him, because he was not a prolific writer. His influence was personal and sprang from his knowledge, character and scientific spirit, his absorbing interest and zeal—it was from those qualities he inspired those who came close to him. His services were of the highest character. Every institution with which he was connected received an impression from him.

Dr. Lambert has indicated the great debt which Columbia University and the Presbyterian Hospital owe to Dr. Janeway. While in New York, he also had to do with the working out of the gift of Mrs. Russell Sage, for promoting scientific medicine. While there he was also elected one of the scientific directors of the Rockefeller Institute, to succeed Dr. Christian Herter, and his voice on our board was always most valuable. On behalf of my colleagues on the board of directors of the Rockefeller Institute for Medical Research, I desire to express our sense of personal loss in his death.

He was a good citizen. He was interested in the modern problems of society and although his devotion to his profession was almost single-minded, he did find time to give to some very interesting social questions and there he rendered great service. He was a good doctor and a good citizen.

We were most fortunate in securing Dr. Janeway as the first professor of medicine under the foundation which enabled this university to institute what we believe to be a great reform in clinical teaching. Through the generosity of the Rockefeller Foundation, we were enabled to establish three of our chairs on what we call the "University Basis." The underlying principle is that in the time to come, those who devote themselves to the responsible work of teaching, to the care of patients in the hospital and to research in the laboratory, shall make that their occupation and life work. The principle appealed to Dr. Janeway and although his experience led him to feel there might be some modifications of certain of the requirements, he was himself and always remained heartily in sympathy with the fundamental conception. I think it was always a great satisfaction to him that he was called upon the first to serve in the most important chair in a medical school—that of Medicine—and to develop the clinic along these newer lines. He rendered unforgettable service in this capacity for which the university must always retain a feeling of gratitude.

If I may be permitted, I would like to emphasize the great service which he, under Col. Bushnell, rendered to our army and therefore to our country. In the opportunities which I have had with General Gorgas in visiting our camps, it has



been the greatest satisfaction to find that there was always a first class medical man at the head of the medical service in the camp hospitals. These physicians and their staffs were selected for this service by Dr. Janeway. He often had to persuade some doctor, usually a successful and active practitioner of the right age for this service, that his duty was to give up his practice and to enter the army for this work. It

is a great satisfaction to all of his friends to feel, as has been so well expressed by the Surgeon General, that he was able to render this great service to his country. He felt intensely about the war and was glad that he had an opportunity to serve. He would not have done differently if he had foreseen all that was to come. I think we may say he died as truly in the service of his country as if he had fallen in battle.

## DR. JOHN HALL: SHAKESPEARE'S SON-IN-LAW<sup>1</sup>

By ELI MOSCHCOWITZ, A. B., M. D.

The physician whose story I propose to tell you to-night was not born great; he did not achieve greatness; he had greatness thrust upon him. He blazed no trail in medicine; nor, like some of our calling who were not even great as doctors, did he distinguish himself in the sister sciences, the arts, the pursuit of the Muses, or the love of his fellow-men. He was just an ordinary general practitioner. He little dreamed, on the day he took Shakespeare's daughter as his bride, that he was rescuing himself from a deserved oblivion.

What then is the purpose of celebrating a person of such slender pretensions to fame? Even the pride we naturally feel that the son-in-law of Shakespeare was a physician would not suffice to commemorate John Hall. It so happens, however, that he wrote a book of case reports gleaned from his own practice, which, medically speaking, is of no value, but yet is of interest to us because it affords a fair record of the state of medical practice in his day. But above all it has an intenser and wider interest, because, avid as we are for every fact, no matter how trivial, that brings us into contact with Shakespeare, this book draws us into a close acquaintance with Shakespeare's family and social circle. And so to-night instead of ranging the Mounts of Olympus, we shall nestle, for a fleeting moment, by the fireside of William Shakespeare.

The direct stimulus to this study was the opportunity to peruse the rare volume written by John Hall and published for the first time in 1657.<sup>2</sup> It is duodecimo, and bears the following inscription on the fly leaf (Fig. 1): "Select observations on English Bodies; or, cures both empericall and historically, performed upon very eminent persons in desperate diseases. First, written in Latine by Mr. John Hall, Physician, living in Stratford upon Avon in Warwick-shire, where he was very famous, as also in the counties adjacent, as appears by these observations drawn out of severall hundreds of his, as choysist. Now put into English for common benefit by James Cooke, Practitioner in Physick, and Chirurgery. London, printed for John Sherley, at Golden Pelican, in Little Brittain, 1657."

John Hall, who married Shakespeare's eldest daughter, Susanna, in her 25th year at Stratford on June 5, 1607, was

born in 1575, and although he was a master of arts, he never attained a medical degree. How he obtained his medical knowledge is not known. In his youth, as usual at that time with people of means, he traveled on the continent. Just when he arrived at Stratford is not known; the first notice of any record of him is his marriage to Susanna, so that it is quite probable that he settled in Stratford only after his marriage. The only other records of Hall during Shakespeare's lifetime, is one in 1611, when his name is found in the list of supporters to a highway bill, and one in 1612, when he leased a small piece of woodland on the outskirts of the town. The Halls lived in a house in the thoroughfare leading to the church in a part of Stratford known as the Old Town. The house is still standing (Fig. 2) and bears the name of Hall's Croft. At all events, here he acquired an extensive practice and bore a considerable local reputation as a skilled physician, as shown by the fact, recorded in his book, that he was often called to treat the Earl or Countess of Northampton, 40 miles away. Dr. Hall apparently was a person of importance in the town of Stratford, for in 1617 and in 1623 he was elected a Burgess, but for unknown reasons he was excused from undertaking office. In 1632, he was again elected and accepted the office. He quarreled with his associates concerning the matter of fines for non-attendance and other matters, and in October, 1633, he was expelled after the following resolution had been passed: "At this Hall, Mr. John Hall is displaced from being a Capitall Burgesse by the Voices and Consent of Nineteene of the Company, as appeared by the letter r at there names, for the breech of orders wilfully, and sundry other misdemeanors contrary to the duty of Burgesse and the oath which he hath taken in this place, and for his continual disturbance at our Halles, as will appear by the particulars." That he was a man of strong passions is also shown by the Linacre professor who translated his book from Latin into English for Dr. Cooke, and who says of him in the preface that "Such as hated him made use of him." The professor probably refers especially to Hall's deep religious convictions. He was an avowed Protestant with puritanical leanings, which became more pronounced as he grew older. Indeed, it is upon Hall, who was executor and, with his wife, residuary legatee of Shakespeare's will, that most of the blame is laid for the loss of Shakespeare's manuscripts of his plays.

<sup>1</sup> Read before the Historical Section of the New York Academy of Medicine, October, 1917.

<sup>2</sup> I am indebted to the Walpole Galleries of New York City for this privilege, for which I thank them.

He died November 25, 1635, and was buried in the parish churchyard. His tombstone records the following inscription: Here lyeth ye Body of John Halle gent. He marr. Susanna daugh. (co-heire) of Will. Shakespare gent. Hee deceased Nove. 25. A: 1635. Aged 60.

Hallius hic situs est, medica celeberrimus arte:  
Expectans regni gaudia laeta Dei;  
Dignus erat meritis qui Nestora vinceret annis,  
In terris omnes sed rapit aequa dies.  
Ne tumulo quid desit, adest fidissima conjux,  
Et vitae comitem nunc quoque; mortis habet

Hall's book, which reports 200 cases, was written in Latin. The manner in which the book was published is interesting and reveals a human touch so Boswellian, that nothing that we know of Shakespeare himself approaches it in intimacy. In 1642, during the Civil Wars, Surgeon Cooke, on duty with a regiment guarding a bridge over the Avon, was acquainted by a friend that Mrs. Hall had some books and manuscripts which her husband had left behind him.<sup>3</sup> He visited her at New Place and, "after a view of them Mrs. Hall told me she had some books left by one that professed physick with her husband for some money. I told her, if I liked them I would give her the money again; she brought them forth, amongst which there was this [referring to the book] with another of the authors both intended for the press. I being acquainted with Mr. Hall's hand, told her that one or two of them were her husbands and showed them her; she denied, I affirmed, till I perceived she began to be offended; at last I returned her the money." This shows, first, that Susanna apparently inherited some of the business acumen of her father. It also reveals that she cared more for money than for books. It also shows that either her education was not sufficient to enable her to detect her own husband's handwriting (her own signature (Fig. 3) reveals anything but a practiced hand), or, that she did not want it to appear that she was willing to part with anything belonging to her husband, to whom, as we shall see, she was closely attached. At all events, Cooke took it to London to have it translated by the Linacre professor mentioned above.

The book evidently had a reasonable popularity, probably as a household manual, for it went into two editions, in 1679 and 1683. Certainly the appeal to the general public must have been very strong, for all the 200 case reports are cures.

From the contents of the book, I gather that Dr. Hall was a general practitioner, with little or no leanings to surgery.

<sup>3</sup> The will of John Hall. "The Last Will and Testament non-cupative of John Hall of Stratford-upon-Avon in the county of Warwick, gentleman, made and declared the five and twentieth of November 1635. Imprimis, I give unto my wife my house in London. Item, I give unto my daughter Nash, my house in Acton. Item, I give unto my daughter Nash, my meadowe. Item, I give my goodes and money unto my wife and my daughter Nash to be equally divided betwixt them. Item,—concerning my study of books, I leave them, sayd he, to you, my son Nash, to dispose of them as you see good. As to my manuscripts, I would have given them to Mr. Boles, if he had been here, but inasmuch as he is not heere present, you may, son Nash, burne them, or doe with them what you please. Witness, thereunto, Thomas Nash, Simon Trapp."

His patients cover a wide social range, including lords, earls, baronets, countesses, squires, Catholicks, goodwives, gentlemen, barbers, maids, household servants and children. The earliest case report of which any date is furnished is that of Lord Compton, who was attended previously to his lordship's departure to Scotland with the king in 1617.

Medically speaking, as I have said, the book is of no value. Dr. Hall was probably no worse and probably a little better than the average country practitioner of his time. The book does not bear evidence of having been written for the eye of the medical fraternity, so that he had little occasion to reveal the depths of his learning. There is no clinical observation, diagnoses are paraphrased into colloquial parlance, the precision of diagnosis seems intended to impress infallibility;—all in all, the case reports are merely the barest outlines and serve as delicate frameworks upon which to hang the elaborate and inevitable cure. The materia medica employed by Hall is extensive, consisting largely of the Galenical plants, with occasionally such mediæval remedies as the dried windpipe of a cock and the dung of various animals. It mirrors largely the therapeutical combination of superstition and empiricism of his time.

The diseases cured by Hall are of the most diverse sort. We may well envy Dr. Hall, who cures by the simplest means diseases in which we, the possessors of a heritage of centuries of the most brilliant discoveries, feel nearly helpless. Thus he reports many cures of dropsy, the falling sickness, melancholy, sterility, enuresis, cancer, etc. Be that as it may, the diseases mentioned in Hall's book cover a wide range. Gynecological diseases are common; postpartum sepsis, sterility, "the whites," dysmenorrhea and menorrhagias. Scurvy seems to have been especially common; also round worms. In addition we find various fevers, including "Enterick" and "Tertian," constipation and other intestinal disorders, especially "the colick," respiratory disorders, gonorrhea, etc.

Commentators have speculated freely upon where Shakespeare derived his amazing knowledge of medicine. I venture to suggest that Shakespeare was indebted largely to Dr. Hall. Certainly he knew his son-in-law for at least nine years, and perhaps longer, before he died, and probably they were no more averse to discussing professional matters with one another, than men in the same professions are to-day. Another leading circumstance, is the fact, as Dr. M. Kahn of this city pointed out to me, that most of Shakespeare's knowledge of things medical is displayed in his tragedies, most of which were written in the later years of his life.

And now we come to the more passionate interest that this book bears. Had Dr. Hall written nothing but the case reports of obscure persons, the book to-day would have been only a curiosity, the mere prey of the collector of Shakesperiana. Fate has so ordained, however, that Dr. Hall happened to include among his case reports the illnesses of persons known to the immortal William himself, so that with another stroke of luck, Hall raises himself from the position of an obscure relative of Shakespeare to the dignity of an historian.

Some were relatives, many were his close friends. Thus we find two references to his daughter Susanna, Hall's wife; Hall's only daughter, Elizabeth, Shakespeare's granddaughter, upon whose death in 1670 Shakespeare's direct lineage ceased; Hall's own sickness is recounted. Also that of Michael Drayton, the poet, with whom Shakespeare and Ben Jonson, according to Vicar Ward's testimony, "had a merrie meeting, but Shakespeare seems drank too hard, for he died of a fever there contracted." This is the only scrap of information we possess of the manner of Shakespeare's death. Indeed, it is not a great stretch of fancy to think that Dr. Hall may have attended Shakespeare during his last illness, and had Hall been as willing to risk his failures as his cures for publication, we might have found Shakespeare's last illness recorded here. We also find the case of Mr. Queeny who was, undoubtedly, that Richard Quiney who died in 1602, and after whose wife Shakespeare's eldest daughter Susanna was named. He was a mercer, and bears the distinction of being the author of the only extant letter to Shakespeare, in which he appealed for a loan of money in 1598. His son, Thomas Quiney, married Shakespeare's second daughter Judith. Mrs. Sadler (p. 13) must have been Judith Sadler after whom Shakespeare's second daughter was named. Hamnet Sadler's name was given to Shakespeare's only son. Hamnet Sadler was an intimate friend and one of the beneficiaries under Shakespeare's will. Anne Ward (p. 212) may have been related to the Vicar of Stratford to whom we are indebted for the only account of Shakespeare's death. A Captain Bassett, who is mentioned twice, may have been the original of the character of that name found in King Henry VI, Part 1.

The following case reports, which have been selected either for their human or their medical interest, serve to indicate the character of Dr. Hall's book:

"Obs. 19. Mrs. Hall of Stratford my wife, being miserably tormented with the colick, was cured as followeth; R Diaphaen. Diacatholic. ana ʒi; Lact. q. s. f. Clyst. This injected gave two stools, yet the pain continued, being but little mitigated, therefore I appointed to inject a pint of sack made hot, this presently brought forth a great deale of wind, and freed her from all pain, to her stomach was applied a plaster de Labd. Cret. cum Canan. et Spec. Aromat. rosat. et Ol. Macis. With one of these glysters I delivered the Earle of Northampton from a grievous colick.

Obs. 36. Elizabeth Hall, my onely daughter was vexed with totura oris or the convulsion of the mouth, and was happily cured as followeth. First I exhibited these pills; R Pil. Coch. et Aureas, ana ʒi; f. pil. 10. She took five the first day which gave her seven stooles. I fomented the part with Theriac. Androniac. and Aq. Vitae. To her neck was used this, R. Lingu. Martiat. Magn. ʒi; Ol. Laverin. petrolei, Castor. et Terebinth. ana ʒi ss de lateribus ʒi; misc. by this she had great advantage, her courses being obstructed, thus I purged her. R. Pil. foetid. ʒi Castor ʒi; de Succin. rhab. egaric. ana ʒi; f. Mass. she took five pills in the morning," etc.

The account of Elizabeth is extremely long, so I shall abbreviate the remainder. On January 5, 1624, she had an ophthalmia. In April she went to London; on the 22d she returned home. She took cold and "fell into the said dis-temper on the contrary side of her face." On May 24 she was attacked by "enterick" fever, which he also duly cured.

I have summarized the report of his own illness, because in the original, it is too long. Pious man that he was, he prefaces his account with a prayer.

Obs. 60. (2) "Thou O Lord who has the power of life and death, and drawest from the fates of death, I confesse without any art or counsell of Man, but only from thy goodness and clemency; Thou has saved me from the bitter and deadly symptoms of a deadly fever, beyond the expectation of all about me, restoring me as it were from the very jaws of death to former health, for which I praise thy name, O most merciful God, and Father of Our Lord Jesus Christ, praying Thee to give me a most thankful heart for this great favor, for which I have cause to admire Thee."

On August 27, 1632, in the 57th year of his age, he had an attack of severe hemorrhoids. He was constipated 14 days; nevertheless, he says, that he "was constrained to visit many of his patients." A fever followed. He first purged with rhubarb. A delirium set in, which was cured by "opening a live pidgeon and applied to his feet to draw down the vapors." At this part of his illness, his wife became alarmed, so two physicians were called into consultation who again purged him fully, and prescribed a formidable host of drugs. In the meantime, "ʒ vii of blood was drawn from the liver veine and leeches were applied to the haemorrhoids." During the convalescence he took Chalybeate Wine as a tonic, and was troubled with a scrotal itch which was cured with a "decoction of sarsaparilla with antiskorbutick herbs."

"Obs. 22. Mr. Drayton an excellent Poet, labouring of a Tertian was cured by the following R. The Emetick infusion; Syrup of violets a spoonfull, mix them; this given, wrought very well both upwards and downwards."

Obs. 38. The report of Mr. Queeney's illness is distinguished by the fact that a troublesome cough was treated with a gunshot prescription containing 28 ingredients. This apparently proved ineffectual, for soon after Dr. Hall ordered his head to be shaved and in addition prescribed four additional prescriptions. Then follows the only report of a fatality throughout the book. "Being not wholly freed from it, he fell into it again next year, all remedies proving successless, he dyed. He was a good wit, expert in tongues and very learned."

I shall cite only a few of the case reports that are of unusual medical interest. Gynecologists may be interested in the three following cases:

"Obs. 52. Mrs. Sheldon, wife to the son, being corpulent, well coloured, was wont to miscarry often, the second month after conception, yet suffered no other accident with it, required my counsel, I advised her to purge, and strengthen the womb, for which she took sage in her drinks and meats, also a little of the following in a raw egg. R Gran. tinctor. Marjorit. tormentilli ana ʒi; Mastic. ʒi ss misc. f. pil. there was given as much as would lie on a groat. For the retaining the infant, this is the best plaster. R Labd. puris. ʒi ss Gallar. Mirtel. Ros. Rub. Sang. Dracon. balanst. ana ʒi ss pil. Naval. ʒi Tereb. ʒi vi Malax. omnia simul, f. Empl. part of which spread on leather, and applied to the loynes, os sacrum, and the bottome of the Belly. This she used all her time, and after brought forth a lusty hearty son, and after that more."

"Obs. 26. Mrs. Broughton of Causon, aged 28. Three days after miscarriage in the fifth moneth fell into a fever accompanied with abundance of after-fluxes, vomiting, loathing, thirst, swoon-



ing, and in danger of death was speedily helpt as followeth. R burnt Hartshorn finely powdered ʒ i; boyl it in three quarts of Spring water till a quart be wasted, then remove it from the fire, after adde syrup of Lemons ʒ ii; rose water ʒ iv, sugar a sufficient quantity. This she drank constantly instead of drink, which gave great ease. The following decoction was given morning and evening, which did cleanse, cure, cast out, and extinguish thirst. R French barley m iv violets P ii, liquiris ʒ iss, jubebs ʒ i; Sebestens ʒ ii; carduus benedictus m iss; make a decoction in sufficient quantity of water to lb xii to the straining, adde sugar of violets and make a drink. By these medicines alone she was cured beyond all expectation."

"Obs. 47. (second series). My Lady Rainsford, beautiful and of a gallant structure of body, near 27, was three days after her being laid of her child, miserably tormented with pain in her belly, from which I delivered with the following. R the white of Hens Dung ʒ i; being put in beer and sugar, she took it. To the belly the following was applied hot. R New milk and Honey, each lb i horehound m i; wheat flour ʒ iii, seffron; ʒ i; boyl them to a pultis. By these she was delivered."

The following reports are of pediatric interest:

"Obs. 35. A child of Mr. Walkers of Ilmington, minister, aged six moneths afflicted with falling-sickness, by consent was thus freed. First, I caused round pieces of piony root to be hanged about the neck, when the fit afflicted I commanded to be applied with a sponge to the nostrils the juyce of Rue mixt with White Wine Vinegar, by the use of which it was presently recovered, and falling into the fit again, it was removed in the same manner. To the region of the heart was applied the following. R Theriac. Ver. ʒ ii Rad. palon. pul. ʒ ss misc. The haire was powdered with powder of the roots of piony and thus the child was delivered from all its fits."

Here is a case that Dr. Cullen might introduce into the next edition of his monumental work on Diseases of the Umbilicus:

"Obs. 98. Dixwell Brunt of Pillerton, aged 3, had a tumor of the navil, out of which broake five long wormes out of a little hole, like a fistula; the nurse pull out four dead, but the fifth was somewhat alive; the forepart moving, the hinder part stirred, as witnessed the nurse, Father, Mother and Maide; the tumor being hard, I appoynted a plaster of hony to be applied, but no wormes appeared; the next day was applied a Cataplasme of green Wormwood, beat with the gall of an oxe, and boyled. There was given a suppository. After these the navil was cured and he lived.

"Obs. 60. Talbot the first born of the Countess of Salisbury, aged about one yeare, being miserably afflicted with a fever and wormes, so that death was only expected, was thus cured. There was first injected a glyster of milk and sugar, this gave two stooles, and brought away four wormes. By the mouth was given Hartshorn burnt, prepared in the farme of a julep. To the pulse was applied, Ungu. Papuleon ʒ ii; mixt with spider's webs and a little powder of nut shells. It was put to one pulse of one wrist one day and to the other the next. To the stomach was applied Mithridate, to the navel the Emplaster against wormes. And thus he became well in three days, for which the Countess returned me many thanks, and gave me a great reward."

Hall was not bound too rigidly by the rules of professional secrecy as the report of the following case reveals. Here is how Hall cures a gonorrhea:

"Obs. 80. William Clavel troubled with a virulent gonorrhea and extreme heat of urine, having been under anothers hands for a moneth without profit was cured with the following remedies in fifteen days space, being in the moneth of November. R Gum

Guaiac pul ʒ i; it was given in beer, it gave five stooles. Afterwards he took a pint of the following decoction morning and night. R Sarsp. ʒ ii; Hermodactyles ʒ iss; Guaiacum, Liquiris, each ʒ i; Seny ʒ i; Seeds of Anis Carraway and Cariander, each ʒ ss; boyl them in eight pints of water till half be wasted. After the strained liquor was taken, there was given the following electuary. R Gum Tragacanth ʒ ss; dissolve it in sufficient quantity of plantain water, strain it, adde gum Guaiacum powdered ʒ ii; Terebinth burnt ʒ i, mix them. Dos. ʒ iss; By the use of the decoction of Sarsa. he was very well purged, and delivered altogether from pain in the loynes and heat of the urine in four dayes, and by the use of the electuary he was altogether cured of his gonorrhoea."

It now only remains, as in the last chapter of a novel, to relate the fate of some of the characters that have passed before our gaze. There is a melancholy interest in this telling, because we find that all of Shakespeare's descendants died before the end of the seventeenth century, so that the most prodigious and universal mind the world has ever known had but a brief blossoming. You may remember that Shakespeare and Anne Hathaway had three children; a son, Hamnet, and two daughters, the younger Judith, the elder Susanna. Hamnet died in his 12th year during the poet's lifetime in 1596. Judith married some two months before the father's death, Thomas Quiney, son of the Richard Quiney mentioned in Dr. Hall's book. The bride was 32 years old; her husband was her junior by four years. Thomas Quiney was a vintner, and became a chamberlain and a Burgess of Stratford. He became involved in much litigation, had financial reverses and moved to London, where, apparently, he died in poverty. The Quineys had three sons, Shakespeare who died in infancy, and Richard and Thomas, who both died soon after reaching manhood. As neither of the latter had issue, the line of the poet in this direction became extinct in 1662 when their mother, aged 77, died.

Of Susanna, Dr. Hall's wife, we know little except that in 1613, during Shakespeare's lifetime, she brought a suit for defamation of character against a John Lane, Jr., who had circulated a libelous rumor of immoral conduct. The slanderer, however, failed to appear, and a sentence of excommunication was passed against him. She died July 11, 1649, and her tombstone is marked with the following verse:

"Witty above her sexe, but that's not all,  
Wise to Salvation was good Mistress Hall,  
Something of Shakespere was in that, but this  
Wholy of him with whom she's now in blisse.  
Then, passenger, ha'st ne're a teare,  
To weepe with her that wept with all?  
That wept, yet set herselfe to chere  
Them up with comforts cordiall.  
Her Love shall live, her mercy spread,  
When thou hast ne're a teare to shed."

The Halls' only child, Elizabeth, was nine year old when her grandfather died. She married in Stratford in 1626, Thomas Nash, a Stratford resident of considerable property. Born in 1593, he was a student at Lincoln's Inn. His father and uncle were intimate friends of Shakespeare. Mrs. Nash became a widow in 1647, and two years later married John Barnard, a

gentleman of wealth. Having no issue by either husband, the last descendant of William Shakespeare died in 1670; and so, like an organ peal in the dusk, the lines of her immortal grandfather's first sonnet serve as a fitting close:

"From fairest creatures we desire increase,  
That thereby beauty's rose might never die,  
But as the ripper should by time decrease  
His tender heir might bear his memory;  
But thou, contracted to thine own bright eyes,  
Feed'st thy light's flame with self-substantial fuel,  
Making a famine where abundance lies,  
Thyself thy foe, to thy sweet self too cruel.

Thou that are now the world's fresh ornament  
And only herald to the gaudy spring,  
Within thine own bud buriest thy content  
And, tender churl, makest waste in niggarding;  
Pity the world, or else this glutton be,  
To eat the world's due, by the grave and thee."

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## PROCEEDINGS OF SOCIETIES

### THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

JANUARY 7, 1918

#### 1. Demonstration of a Duodenectomized Dog. (Abstract.) DR. ERNEST G. GRAY.

In the course of some experiments having to do with the effects of the diversion of the pancreatic juice into the stomach upon the level of gastric acidity it became desirable to extirpate the duodenum. A review of the literature, however, disclosed no record of a successful duodenectomy. This portion of the intestinal tract was first removed by Minkowski, but as his experiments and those of subsequent workers only covered a period of a few weeks no evidence exists concerning the ultimate effects of such an extirpation. The principal reason, probably, why it has been impossible to keep animals living for any considerable length of time following this operation, is that the endeavors to re-establish a channel of communication between the pancreas and the intestinal tract have all been without result.

A new problem then presented itself, the question as to whether the surgical difficulties encountered in the course of the excision of the duodenum might be successfully met. It is the results of some work bearing on this subject to which I wish to refer tonight.

Experiments dealing with this problem were started about a year ago. Of a series of dogs used for this purpose one animal survived the various operative procedures, some died of pneumonia, others of distemper, etc. The extirpation was carried out in three stages. At the first operation the gall-bladder was anastomosed to the proximal jejunum and the common bile duct doubly ligated and divided. Some time subsequent to this the major pancreatic duct was dissected from the duodenal wall and transplanted into the jejunum a short distance from the site of the cholecystenterostomy opening. Then in a third stage the entire duodenum was extirpated and end-to-end anastomosis made between the antrum of the stomach and the proximal jejunum. In order to preserve the vascular supply of the pancreas a very narrow strip of the muscular coat of the duodenum (on the side of the bowel facing the pancreas) was left attached to the pancreatico-duodenal vessels. The margins of this layer of muscle cells were then crushed and stitched together to control bleeding.

The duodenum was removed from the dog which you see before you eight and one-half months ago. Each of the three abdominal wounds healed per primam. Since the resection the animal has gained about 6 ounces in weight (a small fox terrier), his appetite being rather above that of a normal dog. Repeated tests have never revealed the existence of any glycosuria. The stools have been normal in appearance. Throughout the past eight months the dog has continued in excellent health and has always been as active as he appears tonight.

The results of the experimental work just outlined demonstrate conclusively, first, that a dog may remain in good health following a total duodenectomy, and second, that the pancreas may be successfully connected with the intestinal tract after the removal of the entire duodenum.

#### 2. The Origin of the Corpus Luteum. DR. G. W. CORNER, San Francisco, Calif.

#### 3. On the Absorption of Drugs and Poisons from the Vagina. (Abstract.) DR. DAVID I. MACLE.

While a large number of drugs are introduced into the vagina in the form of douches, tampons, suppositories, "uterine wafers," etc., and while a search in clinical literature reveals undoubted cases of poisoning occurring through this channel, no experimental work except that of a clinical character is on record on the subject. In connection with the study of the question of absorption of drugs through unusual channels, the author undertook a systematic study concerning absorption of drugs and poisons from the vagina. A large number of drugs were investigated in this connection: Alkaloids, esters, antiseptics, and dissociable salts. As a criterion or proof of absorption, both physiological and chemical evidence was obtained. It was found that drugs of all kinds are absorbed surprisingly rapidly from the vagina. Thus, for instance, a few milligrams of apomorphin or morphin introduced into the vagina of a dog produced vomiting within five minutes. Among the alkaloids studied were: Morphin, apomorphin, pilocarpine, atropine, cocaine and aconitin. Undoubted proof of absorption of various salts was given by experiments with potassium iodide, potassium ferrocyanide and potassium cyanide. Nitroglycerine is rapidly absorbed from the vagina; so

also are the nitrites of sodium and potassium. Of the antiseptics studied the chief ones were phenol, cresol and corrosive sublimate. All these were found to be very rapidly absorbed as evidenced by physiological and toxicological symptoms and also by chemical tests. The full paper on the subject appears in the *Journal of Pharmacology and Experimental Therapeutics*, Volume X, page 509, January, 1918. In the paper, in addition to the experimental data, an exhaustive review of the clinical evidence is appended and the conclusions reached are as follows:

1. That all kinds of drugs and poisons—alkaloids, inorganic salts, esters and antiseptics—can and are easily absorbed through the vaginal wall.

2. Such absorption is demonstrable by physiological and chemical means.

3. A review of the clinical and toxicological literature shows that poisoning through the vagina of a grave character is not at all uncommon.

4. The experiments reported indicate on the one hand the possibility of rational administration of drugs for therapeutic purposes through the vaginal route; and, on the other hand, emphasize the great danger of indiscriminate employment of various substances in the form of douches, tampons, "uterine wafers," etc.

**3a. On the Absorption of Drugs from the Urethra, Bladder, Ureters and Pelvis of the Kidney. (Abstract.) DR. DAVID I. MACHT.**

Following the report on absorption from the vagina, the author reports studies on absorption from the various parts of the urinary tract. A large number of drugs were studied in this connection. The results may be briefly summarized as follows:

Absorption of drugs from the urethra is very rapid. The posterior urethra, as compared with the anterior one, absorbs more rapidly. As compared with the whole urethra, the absorptive powers of the bladder are surprisingly poor. Thus, for instance, while apomorphin in a dog is rapidly absorbed from the urethra producing vomiting in a few minutes, the same amount and even larger doses of the drug, when introduced into the bladder and prevented from being regurgitated into the urethral canal, produce vomiting after a much longer period of time (half an hour or longer) and sometimes not at all. Among the drugs studied were: Various alkaloids such as morphin, apomorphin, atropin, cocaine, aconitin, pilocarpine, etc.; various salts such as potassium cyanide; and antiseptics such as phenol, resorcin, cresol, etc. Absolute proof is furnished by further experiments that alkaloids and other drugs can be absorbed through the ureters; and some experiments indicate also that absorption may take place from the pelvis of the kidney. The full report of this investigation will be published in several installments in the *Journal of Urology*.

JANUARY 21, 1918

**1. Cinq ans Après. DR. F. C. SHATTUCK, Boston, Mass.**

This article appeared in the April number of the BULLETIN.

**2. Exhibition of a Case of Internal Hydrocephalus. DR. W. E. DANDY.**

This child is presented to the Society because we have reason to believe that it is a case of internal hydrocephalus that has been cured by operation. This statement of course must be accompanied by considerable reservation. Only time will tell whether the result is permanent. We believe the child to be cured: First, because of the tests which Dr. Blackfan and I have been using, and second, on account of the symptomatic improvement that has taken place since operation.

The child came in about three months ago with what proved to be internal hydrocephalus of the obstructive variety. Since this time, the improvement we have been able to note has been one of moving the head from side to side. On admission, the head was a dead weight; he was unable to move it more than a few millimeters. He is now able to hold the head up to a slight extent.

You probably know from the work Dr. Blackfan and I have been doing that there are two types of internal hydrocephalus which can be absolutely differentiated by the phenolsulphone-phthalein test. They are both physiologically similar because both are due to cerebrospinal absorption. In the one type the obstruction is in the intraventricular system; in the other, it is in the subarachnoid space.

This was a case of the obstructive type, and it is only this type which offers any hope of relief by this procedure. The other type may be amenable to treatment, but in an entirely different manner. This is the first case we have had an opportunity to follow and see the results. The operation consisted in the usual cerebellar approach with removal of the occipital bone. We knew from the test that the obstruction was either at the aqueduct of Sylvius or at the basal foramina of Magendie and Luschka. We could not tell at which point until operation.

In one other previous case, we tried to catheterize the aqueduct of Sylvius to relieve obstruction by passing a sound through the aqueduct, being guided only by the sense of touch after passing through the foramen of Magendie. In this case we split the cerebellum and the roof of the fourth ventricle and could see the aqueduct of Sylvius, so that we knew exactly where we were passing our sound. We passed a small catheter through the aqueduct and released an obstruction which was little more than a film. To keep the obstruction open, a tube was introduced. Exactly how to maintain the open aqueduct was a problem. For this purpose, we had to use other surgical observations. Our plan of attack was quite analogous to the line of the procedure against obstruction of the common bile duct. We left the tube in about three weeks. The procedure was accompanied by a fairly severe reaction. Of course we did not know how long the tube should remain in the aqueduct. We were only able to judge by observing the child and its ability to stand reaction. The fontanelles became tense and the child vomited more or less persistently and increasingly. At the end of the three weeks, we decided we should not wait any longer and removed the tube. The symptoms immediately disappeared. That has been nearly a month



ago. We tested the patency of the aqueduct yesterday and found that fluid introduced into the ventricle passes freely into the subarachnoid space. Consequently, we have every reason to believe that the case so far is cured. That is, the ventricles communicate, and it was their failure to do this which caused hydrocephalus in the beginning.

### 3. Visits to Cantonments. (Abstract). DR. WELCH.

It may be worth while to say a few words about some of my experiences of the last few weeks, during which I have had the opportunity of visiting various cantonments. My first visit was in behalf of the Public Health Service to see the work Dr. Goldbacher and his staff had been conducting on pellagra. They have done a splendid piece of work on this very perplexing subject. In my opinion Dr. Goldbacher has shown that the disease is entirely controllable and preventable, both as regards fresh attacks and recurrences.

I was then asked to visit various camps, covering a good deal of territory. The mode of procedure was usually to first pay a call upon the general in command and then upon the division surgeon. Our time was spent with him in inspection of the camp, the infirmaries and in gathering statistics as to the incidence of disease. A good deal of time was also spent in sanitary inspection, and at the base hospital.

As regards the medical organization of the camps, the medical officer in command of the medical service is the division surgeon, who is always a regular army man, a member of the regular army medical corps. It would take very little experience to convince one that no man taken from civil life could possibly fill this position. While professional qualification is fundamental, a man must be a soldier to be a good military medical officer, and the military side of it is just as important as the other. The division surgeons are of the greatest importance and almost without exception they are men of real capacity and fill the positions ably. There is always an aid or assistant to the military surgeon. He is sometimes a medical man, and more frequently also of the regular army.

Then comes the sanitary inspector, who is a very important official. He may be either a member of the regular medical corps, or a member of the reserve corps.

In the base hospitals there is of course the director of the hospital, who is usually a regular army man. His work is mainly administrative. This is quite an important position and is pretty ably filled as a rule. Under the director of the hospital there are the chief of the medical service and the chief of the surgical service. I may say here that any one who has had an opportunity of seeing this organization will realize that Dr. Janeway has done a very great service to his country. At every one of these hospitals there is an unusually good man. That was Dr. Janeway's work in the surgeon general's office, to make sure that there was at least one capable, energetic and enthusiastic young medical man taken from civil life for the purpose of assuming this responsible office. When you see such men as we found in the base hospitals, doing such good work, you are filled with admiration for the work which Dr. Janeway did. As I say, there is in almost every case a good

medical man, and he considers himself fortunate if he can get at least five younger men to look after hearts and lungs, take histories and see to the patients in the wards. I may say that the question of qualifications for these very important positions is regarded as a very serious one in the surgeon general's office.

The older disease which we associated with camp life are no longer those which prevail. What we formerly regarded as the unsanitary condition of camps related to environment, water supply, etc. Today a new group of diseases has taken the place of typhoid fever and dysentery. They are the acute respiratory infections, in which may be included measles and meningococcus infections, and they are conveyed directly or indirectly from person to person. The emphasis is no longer on the type of work done ordinarily by the sanitary inspector in looking after drainage, garbage, etc., important as this work is. All that does not touch these diseases which form a new chapter in military hygiene, a chapter which is divided into two parts: In the first place, more accurate studies of the subject; and in the second, skilled epidemiologists in our camps. It has been arranged that all this work shall be carried out.

FEBRUARY 4, 1918

### 1. A New Hypophysis Operation. Devised by DR. G. J. HEUER. (Presented by DR. W. E. DANDY, in DR. HEUER'S Absence.)

When Dr. Heuer was suddenly called to France last summer, he was prevented from publishing this operation and its presentation will no doubt be deferred until the close of the war. With this in mind, Dr. Halsted thought that priority should no longer be risked, and suggested that I present the salient features of the operation before this Society.

As you know, numerous operations have been devised for hypophyseal tumors: McArthur's and Frazier's through the roof of the cranium; Dr. Cushing's removal of the floor of the sella turcica; and various others. None of them, however, are really more than an *approach* to the hypophysis; that is, after the gland has been exposed, the operator has had to desist without attempting to remove the tumor. At most, only a fragment could be removed, and this, only sufficient to make a diagnosis, offered no therapeutic benefit to the patient. Dr. Heuer's operation really opens up a new field for hypophyseal tumors. Up to this time none of the operations have given any way of successfully removing a hypophyseal tumor. The exposure was too limited and nothing could be accomplished except in a very few cases in which a cyst was present which could be punctured.

By this new operation, it is possible to thoroughly expose the hypophyseal region, to expose the tumor and to determine whether it is or is not enucleable. If the former, it can be removed by this method. We have employed this mode of procedure in about 20 cases. I think the operation can best be demonstrated by means of a few slides which will be shown.

The first slide shows the outline of the incision. It consists of a very large bone flap carried well toward the supraorbital margin, with the base parallel to the zygoma. With a very

large bone flap turned down and the dura similarly incised, there is sufficient relief of pressure from an intracranial tumor to allow approach to the hypophyseal region and give sufficient room for exploration.

The second slide shows a tumor protruding between the optic nerves at their point of entrance into the optic foramen.

The third slide shows a tumor removed, with the optic nerves intact. The tumor is shelled out in the space between the two optic nerves.

Hypophyseal tumors have been the most discouraging part of neurological surgery and until the advent of this operation it seemed almost useless to operate, because there was nothing one could do except in the rare instances of hypophyseal cyst. Now the prospects are very much brighter and we feel discouraged if we are not able to take out the tumor. Of course, there are various types of tumors and the differentiation can be made only by operation, but by operating one can absolutely decide whether or not it is possible to remove the tumor. This can be done in no other way except by this operation devised by Dr. Heuer.

2. **Observations upon the Pathology of Diabetes.** DR. FREDERICK M. ALLEN, Rockefeller Institute for Medical Research.

3. **Results of Past Methods and To-Day's Problems in the Treatment of Diabetes.** DR. ELLIOTT P. JOSLIN, Boston, Mass.

This article appeared in the April number of the BULLETIN.

#### THE JOHNS HOPKINS HOSPITAL HISTORICAL CLUB

JANUARY 14, 1918

1. **The Historical Section of the Royal Society of Medicine in London.** Extract from Dr. Fletcher's Letter to Dr. Hurd, December 16, 1917.

I am glad to know that the Medical and Historical Societies are still "carrying on."

Sir William Osler lets me know the dates of the meetings of the Historical Section of the Royal Society of Medicine, at their fine new building at 1 Wimpole Street, and I have been up twice. The meetings are at 5 o'clock, and as the Englishman can't get along without his afternoon tea, tea is always served before the meeting at 4.30. At the October meeting I met Colonel Adami, who is connected with the D. M. S. Office, Col. Darcy Power, Dr. Norman Moore, Professor Cushney, and others. This meeting was given over to Boerhaave. Sir William read the first paper—an excellent one—and showed the Boerhaave treasures, bought at Leyden when he made the pilgrimage there with Doctor Dock many years ago. The second paper was by a Leyden professor, but was read by the secretary, as the professor could not come. The perils of the North Sea are not conducive to travel at present. The last one was by Col. Darcy Power, and consisted of a translation of many of Boerhaave's letters to an English correspondent. Dr. Norman Moore entered into the discussion.

The November meeting was a joint one of the British Folklore Society and the Historical Society, and the paper was by the president of the former, an Oxford anthropologist. Title: "The Primitive Medicine Man." It was interesting, but as is often the case, Sir William's discussion was even more so.

Tom McCrae probably gave you a very good idea of the character of the work here. He left a splendid reputation behind him, as we would naturally expect. We are kept busy all the time. The 2080 beds are always practically all occupied. No sooner are evacuations made, than their places are taken by fresh convoys. Surgical cases predominate, but we always have from 600 to 900 medicals. The purely medical problems are largely those of a large hospital, although we have cases naturally not incidental to civil life, interesting perforating wounds of the chest, gassed cases, and trench fever, trench nephritis, etc.

The Russian collapse and the Italian retreat were very depressing. I am always hopeful, and if the French, Italians and British can hold their lines until the spring, I don't think for a moment that there will be any question of the ultimate outcome. The weight of the United States is bound to turn the scales, and all the editorial writers and military critics over here are most complimentary in their comments regarding the thorough way the United States has gone into the preparations for carrying on her share of the conflict.

The taking of Jerusalem has been a cheering bit of news. Its capture and that of Bagdad has helped to restore British prestige in the Mohammedan world. It had been badly shattered by the Gallipoli campaign.

Germany will make big efforts to break down the Allies before the United States can come in, but I think that a lot of what they say they are going to do is largely bluff.

I have had correspondence with Dr. Fayerweather, who is doing excellent work at a large orthopaedic hospital at Leeds. I unfortunately missed seeing Dr. Young and Dr. Baer in London when they were there a few weeks ago. Being in the Imperial (Canadian) Service, I haven't the chance to meet as many of the Americans as I should like. Dr. Hall was down and spent a Sunday with us several weeks ago.

## NEW PUBLICATIONS.

The following six monographs:

**Free Thrombi and Ball-Thrombi in the Heart.** By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

**Benzol as a Leucotoxin.** By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

**Primary Carcinoma of the Liver.** By M. C. WINTERITZ, M. D. 42 pages. Price, 75 cents.

**The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911.** By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

**The Origin and Development of the Lymphatic System.** By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

**The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale.** By EDWARD F. MALONE, M. D. Price, \$1.50.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

## NOTES ON NEW BOOKS.

*Burdett's Hospitals and Charities, 1917.* Being the Year Book of Philanthropy and the Hospital Annual containing a review of the position and requirements and chapters on the management, revenue and cost of the charities, an exhaustive record of hospital work for the year, etc. Twenty-eighth year. By SIR HENRY BURDETT, K. C. B., K. C. V. O., etc. (London: The Scientific Press, Limited, 28 & 29 Southampton St., Strand, W. C.)

The somewhat tardy appearance of this annual volume is explained by the editor as due to difficulties incident to the war. We are promised that the volume for 1918 will be more promptly issued. We regret to see that Sir Henry Burdett speaks again of his desire to secure a competent person to relieve him of the labor which has borne heavily upon him for nearly 30 years. It is very doubtful whether any person can be found who has the same familiarity with the broader aspects of charity or an equal grasp of the practical details of hospital management. We trust that he may long continue to edit the work.

Probably the most interesting portion of the present volume is the chapter referring to hospital incomes and expenditures. The figures and facts presented show an unparalleled increase in the expenditures of all hospitals and corresponding increase of income. In many hospitals the income has doubled in the past 20 years, but outlay for supplies has more than kept pace with the increase of income. The increase of income has been derived from increased contributions on the part of the former contributors to hospitals, and also from grants from the government for the care of invalided officers and soldiers. The increase of expenditures is due to the higher cost of food, fuel, labor, medicines and supplies of every sort. Many articles of food have increased in price three-fold, and of medicines and apparatus ten-fold. There have also been serious difficulties in the training of nurses for service abroad, and many increased expenditures due to the increase in the number of nurses required, and the cost of their supplies and equipment.

Another interesting chapter relates to the provision made for the care and training of those persons blinded in army service. It is most gratifying to read of the efforts made not only to care for the blind in their helplessness but also to fit them for self-support. It is not enough to make them comfortable. They must be made cheerful and self-respecting by instruction in trades and industries until they are capable of self-support wholly or in part.

Many old time topics are touched upon in the volume, such as the need of uniformity of accounts in institutions, the need of uniformity in training nurses, etc. The book is of great value, and should be in the hands of all hospital officers. We have nothing to compare with it in America. H. M. H.

*Nutrition and Clinical Dietetics.* By HERBERT S. CARTER, M. A., M. D.; PAUL E. HOWE, M. A., PH. D., and HOWARD H. MASON, A. B., M. D. Cloth \$5.50. (Philadelphia and New York: Lea & Febiger, 1917.)

This book furnishes a very welcome addition to the literature on nutrition and clinical dietetics. There is no branch of therapeutics which has been neglected more than diet. It has been only slowly realized that the administration of food, in disease or in health, is not a matter of common sense and intuition, but should depend upon an accurate knowledge of pathological physiology. Unfortunately, many of these underlying principles remain to be determined and consequently, when diets are ordered in the sick room, great discrimination and judgment are necessary.

Carter, Howe and Mason have produced an admirable volume. They have kept the scientific limitations of the subject in mind. Throughout they have furnished a very satisfactory and readable summary of the facts in each instance, and have based the diets advocated as far as possible on their conclusions. It is a pleasure to order diets under such directions.

Part I furnishes a simple yet forceful exposition of digestion, food requirements, normal feeding and food economics. The last is a particularly timely subject and is well, even if briefly, presented.

Part II treats of the value of the foodstuffs, proteins, fats, etc., in the diet, and the availability of these materials in various products. This section is of great importance to those who wish to understand thoroughly the subject of practical dietetics.

Part III takes up in a very satisfactory manner the troublesome question of feeding in infancy and childhood.

Part IV, devoted to feeding in disease, furnishes the major portion of the book. In these chapters the sound application of scientific knowledge to practical dietetics is the dominant note. Consequently, the author escapes many of the fallacies previously recorded, and succeeds in presenting a most useful and thoroughly up-to-date guide in this field. There is not an absolutely even distribution of effort among the various chapters, some subjects receiving more detailed attention than others.

## BOOKS RECEIVED

*Experiments with Oxygen on Disease; Tuberculosis.* Bright's Disease, et al. By James Todd, A. M. 1916. 8°. 225 pages. Published by the author, Pittsburgh, Pa.

*Diseases of the Chest and the Principles of Physical Diagnosis.* By George William Norris, A. B., M. D. and Henry R. M. Landis, A. B., M. D. With a chapter on the Electrocardiograph in Heart Disease, by Edward B. Krumbhaar, Ph. D., M. D. 1917. 8°. 782 pages. W. B. Saunders Company, Philadelphia and London.

*Technic of the Irrigation Treatment of Wounds by the Carrel Method.* By J. Dumas and Anne Carrel. Authorized translation by Adrian V. S. Lambert, M. D., with an introduction by W. W. Keen, M. D., LL. D., F. R. C. S. (Hon.). 1917. 12°. 90 pages. Paul B. Hoeber, New York.

*Food for the Sick; a Manual for Physician and Patient.* By Solomon Strouse, M. D., and Maude A. Perry, A. B. 1917. 12°. 270 pages. W. B. Saunders Company, Philadelphia and London.

*International Clinics.* A Quarterly of illustrated Clinical Lectures and Especially Prepared Original Articles. By Leading Members of the Medical Profession Throughout the World. Edited by H. R. M. Landis, M. D. Volume IV. Twenty-seventh series. 1917. 8°. 314 pages. J. B. Lippincott Company, Philadelphia and London.

*A Treatise on Regional Surgery.* By Various Authors. Edited by John Fairbairn Binnie, A. M., C. M., F. A. C. S. Volume III. With 521 illustrations. 1917. 8°. 830 pages. P. Blakiston's Son & Co., Philadelphia.



# BULLETIN

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## PREPARATION OF U. S. ARMY TRIPLE TYPHOID VACCINE<sup>1</sup>

By MAJOR C. G. SNOW,

*Army Medical School, Washington, D. C.*

This vaccine contains five strains of typhoid and paratyphoid bacilli. Of the former only the Rawlings strain, of the latter four; Rogers and Meers Para "A," and Cools and Rowlands Para "B." The Meers and Rowlands strains were secured from England and are the strains used in the English vaccine.

The preparation of vaccine on the large scale now required by the army demands many steps that are found unnecessary when only small amounts are made—steps that may perhaps appear superfluous at first but which assume vital importance when the output must run to thousands of liters monthly. In the description given below of the preparation of typhoid and triple typhoid vaccine as made in the Army Medical School, the commercialized technic required in handling this vast quantity is given with as much detail as space and time will allow.

It is hardly necessary to state that the principles and scientific facts that are commercially applied are those originally promulgated by Colonel F. F. Russell, Medical Corps, U. S. A., who may well be called the "father of typhoid vaccine"; and the most casual glance at army and navy statistics is all that

is required to prove the accuracy of these principles. Following Colonel Russell came such men as Lieut.-Colonel Whitmore, Major Nichols and Major Reasoner, who devoted countless months and untiring labor that the army vaccine should go forth in any amount required with the standard unchanged. There is no doubt that time and greater experience will disclose new methods, possibly largely mechanical devices, that will greatly simplify our present technic without in any way lowering the quality of the vaccine. In fact many such devices and technical changes are at present under consideration, that are theoretically correct and practical, but in times of stress such as these we dare not introduce radical innovations in so important a process, which have not been thoroughly tested by the results they exhibit when clinically applied. For we know the success of the present vaccine and that it affords a satisfactory prevention, and we know also that under the present system it can be produced in the amounts required, so, until the times comes when a new process shall have been equally well tried we must, for the sake of our men, retain our somewhat cumbersome technic.

For the sake of description it may be convenient to divide this subject into the various sub-headings or sections used in handling this problem in the Army Medical School.

<sup>1</sup>Read before The Johns Hopkins Hospital Medical Society, December 17, 1917.

## PREPARATION DEPARTMENT

In a general way this department is housed in three main rooms in which all the material used in the production of army vaccine is assembled and placed in proper condition. The glass-ware is sterilized, the agar made, and the cleansing of apparatus attended to. One room is devoted chiefly to hot-air sterilization, another to autoclave sterilization and the preparation of media, and the third to salt solution. Necessarily there is considerable overlapping of the duties of the men assigned to these three rooms, but as far as possible they are kept separate. All sterilization is done immediately prior to the use of the apparatus in question, and in the case of the ampoules they are always taken directly from the sterilizers to the filling and sealing room.

The medium used is ordinary nutrient agar made with Liebig's Beef Extract and Witte's peptone, the reaction being carefully adjusted to 1.0 per cent acid. The salt solution is used in 0.85 per cent strength made from chemically pure sodium chloride and distilled water. It is filtered through paper directly into one-liter flasks and sterilized in the autoclave. Following sterilization of the salt solution it is tested for sterility and never used when over 36 hours old. The agar, after preparation, is placed in Kolle flasks, 45-50 c. c. in each flask, sterilized in the autoclave and then allowed to incubate until inoculated. It is very unusual to find either agar or salt solution contaminated, for which thanks are due to those assistants who have this directly in charge.

## CARE OF THE CULTURES

Three sets of three tubes each of the five cultures used in the preparation of this vaccine are kept constantly under lock and key, and only one of these is used for the routine work, the two remaining sets being kept in locations known only to the officer directly in charge. From these original cultures transplants are made, originals renewed, and working plates prepared every week or 10 days. From the stock plates individual colonies are transferred to large agar slants and double sugar tubes, the former being used to prepare the planting emulsion, and from the latter agglutinations and stains are made to test the purity of the transplanted colony. For the agglutination we use a 1:1000 dilution of a known serum having a titer of 1:5000 with a cross agglutinating index never higher than 1:300 and rarely this high.

In the preparation of plates, transfer of cultures, fishing of colonies, preparation of planting emulsion, and the agglutinations, the work is always done by two men, the officer in direct charge and one assistant, and a very careful double check is kept to avoid the possibility of a mistake. It is very essential that the stock plates from which transplants are made shall have distinct and clearly isolated colonies so that in subsequent utilization there can be no possible confusion.

The preliminary steps in the preparation of vaccine, which have been merely indicated, will be found to require a great many assistants and the expenditure of much time and labor,

and too great emphasis cannot be laid on these stages of the process as errors here will render futile all subsequent work. The timing of these preliminary steps alone, while seemingly very simple, requires constant care and the closest application.

## INOCULATION OF FLASKS

As a routine, runs of from 2000 to 3000 flasks are made. This number, of course, requires a much larger incubating space than is supplied by the ordinary laboratory incubator and as a consequence it was found necessary to build a completely insulated room 8 ft. x 19 ft. x 12 ft. heated by 14 separate electric stove units, controlled by a thermostat and solenoid. As about 12 men are required in handling this number of flasks, and as more than six men should not be allowed to work in a room of the ordinary size, it was found necessary to establish two vaccine rooms opening directly on the incubating room. The fact that 24 hours is the minimum time required for the growth, and that the washing stage consumes about 14 hours, makes it necessary to start inoculating not later than 4 o'clock in the morning. The emulsions, however, must be prepared prior to this and it is our custom to start this process at 3 o'clock a. m. At this time the officer in direct charge and one assistant enter one of the vaccine rooms and, under as nearly as possible complete asepsis emulsify the growth from the massive agar slants above spoken of. This process is simple but requires extreme care, the slants after a thorough burning of the cotton stoppers and the mouths of the tubes are treated with about 15 c. c. of sterile broth which, after soaking for a few minutes, allows the growth to be removed by rapid rotation of the tube. This emulsion is then transferred to one or two large-sized tubes containing a similar broth, each of these tubes receiving a number designating the section it is to inoculate. Ordinarily one colony inoculates two sections, quite frequently only one, and sometimes three.

In this work a record sheet which has been previously prepared is very carefully followed (see Table 1). While this process is going on, the remainder of the assistants have entered the incubating room from another door than the one communicating with the room where the above work is being done and are burning the stoppers of the flasks *en masse*, the flame being extinguished as soon as possible with a moist antiseptic towel. During this stage the cotton stoppers are not removed. As soon as these flasks are burned other assistants stack them in wooden racks holding 50 flasks, each rack constituting one section. Half of the total number of sections desired are transferred to the unused vaccine room, by which time the emulsions are completed and the room in which this work was done is prepared for work. All who are to work in the inoculation now clothe themselves in sterile cap, gown, and rubber gloves. The inoculating apparatus consists of a small brass tube-holder with a protecting shield of antiseptic gauze, a sterile cotton swab and a Bunsen burner. The burning of cotton having been done previously, the stoppers are removed and direct inoculation made to the agar surface with the swab which is refreshed in the emulsion tube after each flask. The mouth of the flask

must be thoroughly and symmetrically flamed prior to inoculation and the greatest possible care used to contaminate neither the swab nor the emulsion tube. In this way the entire section is planted and restacked in an empty rack. The topmost flasks are marked with the section number and the inoculators' initials; the latter going also on the record sheet, thus showing by whom each section has been inoculated. When all sections

TABLE I

Run of Jan. 18-19, 1918	Strain	Section	No. flasks	Inoculator	Washer	Count	Strength	No. bottles.	Tricresol per bottle	Salt solution per bottle	Vaccine per bottle
Typhoid No. 283	Rawlings	1	50	A	Q	5500	2000	1	13.7	3500	5500
		2	50	B	R						
		3	50	C	Z						
		4	50	D	T						
		5	50	E	and						
		6	50	F	so						
		7	50	G	on						
		8	50	H							
		9	50	I							
		10	50	J							
		11	50	K							
		12	50	L							
		13	50	M							
		14	50	N							
		15	50	O							
		16	50	P							
		17	50	Q							
		18	50	R							
		19	50	S							
		20	50	T							
		21	50	U							
		22	50	V							
		23	50	W							
		24	50	X							
		25	50	Y							
		26	50	Z							
		27	50	A							
		28	50	B							
		29	50	C							
		30	50	D							
Para. "A" No. 85	Rogers	31	50	V	Z	6600	3000	1	11.0	2400	4400
		32	50	Q	X						
		33	50	P	X						
		34	50	P	X						
		35	50								
		36	50								
		37	50								
		38	50								
		39	50								
		40	50								
Para. "B" No. 51	Meers	41	50	St.	Pa.	6000	3000	1	11.5	2600	4600
		42	50	Na.	Ny.						
		43	50		Zeo.						
		44	50								
		45	50								
		46	50								
Para. "C" No. 51	Cools	47	50	Co.	Co.	6000	3000	1	11.5	2600	4600
		48	50	Je.	Pen.						
		49	50	Ka.	Gil.						
		50	50								
		51	50								
		52	50								
		53	50								
		54	50	Jk.	Tm.	7500	3000	1	12.5	3000	5000
		55	50	No.	Pq.						
		56	50								
Para. "D" No. 51	Rowlands	57	50								
		58	50								
		59	50								
		60	50								
		61	50								

are complete, they are returned in the racks to the incubating room. New swabs and emulsion tubes are used for each section.

One of the most difficult things to teach the beginner in inoculation is the necessity of covering the entire surface of the agar, which can be done only by establishing a definite method of procedure and constantly adhering to it, because, if the agar is properly prepared, the passage of the swab over it leaves no mark. In this procedure absolute asepsis is essential, rubber gloves must be worn at all times and as little movement as

possible allowed in the room. Exposed agar Petri dishes are placed beside each worker to obtain a partial control of the number of air colonies near his emulsion tube.

## WASHING

Under this caption we designate that stage of the process wherein the growth, after approximately 24 hours of incubation, is removed from the agar and placed in large collecting flasks for heating. Each section of 50 flasks is treated with a total of slightly less than two liters of 0.85 per cent salt solution. This is done by removing the cotton plug from an individual flask the mouth of which is well flamed, and pouring in a quantity of salt solution the amount of which must be learned by experience, so that all flasks of the section may receive a sufficient amount of solution for washing purposes without any running over the two-liter mark. The flask is then placed agar down to allow the liquid to soften the growth. All flasks of the section, after being treated as above described, are scraped, beginning with the flask first receiving salt solution. During the scraping or the removal of the growth from the agar the flasks are constantly rocked backwards and forwards, allowing the salt solution to thoroughly rinse off the growth; they are then set in an upright position in an especially designed wooden rack to facilitate draining of the emulsion from the somewhat sticky medium. The contents of these flasks are now poured into two-liter Erlenmeyer flasks designated as collecting flasks, each being marked at the two-liter level. The deficiency in volume is now made up from a sterile salt solution flask. The collecting flask is now marked with the section number and the name of the man who washed it, this same information being transferred to the record sheet. About 5 c. c. of the emulsion are now removed from the collecting flask for standardization following which the cotton stoppers are well protected with sterile tinfoil. When a sufficient number of flasks have been secured they are placed in a water-bath the temperature of which is carefully adjusted to 52.6° C. Here they are left for one hour. There are three important rules that must be followed in this stage of the process: First, be sure to remove all the growth; second, do not scrape off any agar; third, absolute asepsis.

Many different appliances have been suggested for use in removing the growth from the Kolle flasks, but we have found the one most simple and satisfactory to consist of a large platinum loop averaging from 2 to 3 cm. in diameter.

The water-bath in which the emulsion is heated was especially designed for this purpose. It consists of a circular tank in which a constant circulation of water is maintained by an electrically actuated propeller. In this bath one control flask is kept constantly with a thermometer which registers as nearly as possible the mean temperature of the vaccine emulsion.<sup>2</sup>

While the emulsion is being heated, standardization goes on, the counting being by the Wright system and Wright's stain

<sup>2</sup> Another thermometer registers the temperature of the water outside the flasks.



being employed. It has been found from experience that this technic, if properly applied, is entirely satisfactory and, inasmuch as since the beginning of vaccine preparation by the army this method has been followed, it is not deemed advisable to introduce any change, owing to the danger of altering the present standard of the vaccine. One or two rather minor points in this step are worthy of mention, the first and most important being that from the time counting is started until the completely stained slide is under the microscope, the greater the speed the more accurate the results; another is the size of the drop of blood and emulsion mixture used, which must be small enough to allow it to be completely spread over the slide so that there is no surplus. One great drawback in this method of standardization is the fact that most army men have been repeatedly vaccinated and consequently have a rather high agglutinating index. This applies to men constantly associated with the preparation of typhoid vaccine particularly, for we find from practical experience that those of us who are so associated present a very erratic and troublesome agglutination. These agglutinations on the slide frequently cause the counter many troublesome hours. In so far as possible the standardization is always done by the officer in charge, who uses his own blood with the agglutinating index of which he must of necessity become very familiar.

#### CULTURING THE HEATED VACCINE

While the standardization and heating is under way, another group of assistants clean out the vaccine room and place it in proper condition for use in culturing and diluting. The two-liter collecting flasks containing the pure emulsion are then transferred to this newly prepared room and the tinfoil on the tops is removed. Tubes of melted agar, sterile Petri dishes, and pipettes are now assembled and from each of the collecting flasks under the strictest precautions, samples of the emulsion are removed and plated for purity, a portion of this sample being retained for subsequent examination should the need arise.

#### DILUTING

The stock vaccine is carried in the following dilutions: Typhoid 2000 million per c. c.; paratyphoid "A" and "B" 3000 million per c. c. The actual strength of emulsion per c. c. for each individual flask having been determined previously by standardization, the necessary amount of salt solution to be added to make the total equal the desired strength is easily determined. Inasmuch as the vaccine is to be preserved in 0.25 per cent tricresol, the proper amount of this reagent and of salt solution is added to each of the stock bottles and thoroughly mixed. Stock bottles used for this purpose have the capacity of 8, 12, and 16 liters and are made from carefully selected glass, plugged with cotton and thoroughly sterilized in the autoclave. Prior to the addition of either tricresol or salt solution each bottle is designated by a tag bearing the number of the vaccine run, the section, strain, the date when made, and the amount

and strength of the vaccine it contains. To render mistakes less likely, the tags for the different strains vary in color, typhoid being white, paratyphoid "A" yellow, and paratyphoid "B" green. Following the heating, and the preparation of the stock bottles with the proper amount of tricresol and salt solution the emulsion is poured into the stock bottles with the usual degree of care as to asepsis. Each stock bottle now contains from 3 to 7 liters of the finished vaccine which, after thorough mixing, is allowed to remain at the temperature of the vaccine room, which is approximately 105° F. at this time, for two hours. It will be seen from the above statement that each stock bottle represents one section. At the end of these two hours cultures are again made, this time including two plates and an anaërobie tube, 2 c. c. of the vaccine being used in each, and 5 c. c. placed in a sterile tube for future examination should need arise, and for animal inoculation. For the latter the vaccine is pooled and injected into mice, guinea-pigs, and rabbits. The doses used are of the same size as those given to man and in the case of the rabbit and mouse are subcutaneous and in the guinea-pig intraperitoneal, the exception being that in this last dose the quantity is 1500 million whereas the others are 500 million. A single dose only is used for the mouse and the guinea-pig, whereas 10 days after the first injection of the rabbit it receives a second dose of 500 million and 10 days following this is bled to determine the agglutinating index.

Following the plating of the tricresol-killed vaccine the mouths of the stock bottles are protected with tinfoil and returned immediately to the ice-box where they remain until the cultural and animal controls have determined their purity. This period varies, but is never less than five days and very frequently considerably longer. This step concludes the actual preparation of the vaccine, but is necessarily followed by appropriate mixing, amputing, and testing of the final result.

#### MIXING

It having been decided that it was better to administer the three organisms as a single vaccine, it became necessary to mix the various strains and as a consequence convenient dilutions were decided upon as a standard for the stock vaccine. These dilutions have been noted above and allow of the typhoid and paratyphoid strains being mixed in equal volume, which from a practical standpoint greatly facilitates accuracy and speed. One part of each of the paratyphoids being mixed with four parts of typhoid gives a resultant dilution in which each cubic centimeter contains 375 million each of the paratyphoid strains and 1000 million of typhoid. This mixing is done entirely by four men, trained and trusted assistants of this department. The vaccine is measured from large stock bottles into sterile two-liter graduates, from which it is transferred to other stock bottles bearing an appropriate label for the vaccine contained. Records of this mixing are made and kept in permanent file from which it would be possible to trace back to the source any error that might arise, though the number of controls and checks that are made practically prohibit any

such accident. Following this mixing, aerobic and anaerobic cultures are made and the vaccine is not used for ampouling until after the sterility of the mixture has been definitely determined. As regards the reading of all culture control plates and tubes there is one unvarying law followed, *i. e.*, "If any doubt exists, discard the vaccine." Readings of all the culture plates and tubes are invariably made by the four men above referred to and any difference in opinion is considered sufficient evidence to warrant the discard of the vaccine resulting from the section in question.

#### AMPOULING

After the mixed vaccine has been released, which is never done until both the aerobic plates and anaerobic tubes have been incubated at a minimum of 24 hours, it is turned over to the ampouling department and, as in all other departments, absolute asepsis is preserved as far as possible. This work is done by men clothed in sterile cap, gown, and rubber gloves. The ampoules are taken immediately from the hot-air sterilizers to the sealing-room where they are at once filled and sealed. At no time are the ampoules, either filled or unfilled, allowed to stand uncovered. In this department also the arrangement of the vaccine into sections is strictly observed. Here one section

representing one bottle that exactly corresponds in name and number with the original section planted may be traced back in case of contamination by means of the record sheet and in this way it is possible to recognize every one through whose hands it may have passed. The ampoules representing each bottle or section are packed in especially prepared cartons and three samples from each section removed for cultural examination. The packed cartons representing now the original sections are kept separate from each other until the cultural tests both aerobic and anaerobic have been determined by examination after 48 hours to be sterile. Following this the vaccine is finally released for issue. In addition to the above rather elaborate controls that have been indicated, there are others which it is unnecessary to mention.

This very brief account of army vaccine is given merely as an introduction to the motion picture illustrations of each stage of this process. Many minor points in the technic must be ignored at the present time as their description would be practically an impossibility. Difficulties are constantly arising that must be overcome, accidents occurring that must be remedied, and quick and safe judgments constantly made. We have but one rule to guide us and this we attempt to follow: "Work hard and make no mistakes."

## THE INFLUENCE OF MENSTRUATION ON ACIDOSIS IN DIABETES MELLITUS. REPORT OF A CASE<sup>1</sup>

By GEORGE A. HARROP, JR., and HERMAN O. MOSENTHAL

Menstruation has not been regarded as a factor which influences the course of diabetes mellitus appreciably. Naunyn<sup>2</sup> quotes Lecorché as claiming that menstruation has a tendency to diminish glycosuria. Naunyn's own experience evidently points in exactly the opposite direction. We have not been able to find any allusions to the effect that menstruation may have on acidosis. The report of the present case is of interest in this connection. The history and the physical examination of this patient were as follows:

H. L., Medical No. 38691.—Colored; aged 18; schoolgirl. Admitted September 21, 1917. Discharged November 11, 1917. Died November 27, 1917.

*Family History.*—Not important.

*Past History.*—Essentially negative. Menstruation began at 15. The periods were regular, but often lasted for a week. They were accompanied by a good deal of dysmenorrhea. Her best weight before onset of the diabetes was 101 pounds.

*Present Illness.*—The first definite symptom of diabetes was polyuria, which was noticed one year ago and has gradually become more marked, until now she voids every hour or two during the day and night. At about the same time she began to lose weight, and to feel drowsy and listless. She grew irritable and complained of pains in the legs, and later in the back. Her appetite has become enormous and she has had excessive thirst. During

the past few months her menses have become more irregular. The last period occurred about two weeks prior to her admission and lasted a week. During the last three or four days of menstruation, the mother states, the girl was very drowsy, she had no desire for food, she complained of abdominal pain, her breathing was deep, and the amount of urine voided during this time was much less than usual.

*Physical Examination.*—Height 5 feet 1½ inches. Weight 72½ pounds. A thin, undernourished colored girl. The pupils are equal and react to light. Marked pyorrhea alveolaris. Heart and lungs clear. Abdomen negative; liver and spleen not enlarged. Thyroid isthmus palpable, and contains a pea-sized nodule. Knee-jerks absent. There are no motor or sensory disturbances.

*Blood Examination.*—W. B. C., 7900. R. B. C., 5,200,000. Hemoglobin (Sahli), 78 per cent. Wassermann reaction negative. Blood sugar on admission, 0.148 per cent.

Throughout these studies the nitrogen was determined by the Kjeldahl method, the urinary ammonia by Steel's modification of Folin's method,<sup>3</sup> the urinary glucose of Benedict's modification of Fehling's solution,<sup>4</sup> the acetone substances in the urine by Shaffer's<sup>5</sup> procedure, the blood sugar by the method of Lewis and Benedict,<sup>6</sup> the tension of carbon dioxide

<sup>1</sup> Steel, M.: Jour. Biol. Chem., 1910, VIII, 365.

<sup>2</sup> Benedict, S. R.: Jour. Am. Med. Assn., 1911, LVII, 1193.

<sup>3</sup> Shaffer, P. A.: Jour. Biol. Chem., 1908, V, 211.

<sup>4</sup> Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, XX, 61.

<sup>5</sup> From the Medical Clinic of The Johns Hopkins Hospital.

<sup>6</sup> Naunyn, B.: Der Diabetes Mellitus. Wien, 1906, p. 235.

in the alveolar air according to Marriott,<sup>1</sup> and the food values were calculated from the tables of Atwater and Bryant.<sup>2</sup>

From Table I, it is readily appreciated that this girl entered the hospital suffering from a very severe type of diabetes mellitus, accompanied by a marked degree of acidosis. The urine could be rendered sugar-free only temporarily by means of starvation; the acid substances in the urine were fairly high, the percentage of ammonia nitrogen of the total urinary nitrogen was well above the normal, and the carbon dioxide tension of the alveolar air was low, in spite of the large amounts of bicar-

On the 28th of October, with the onset of the menstrual period, the picture changed completely. On that day she complained of abdominal pain and refused food. At 7 p. m. a change in the character of the breathing, with increasing drowsiness, was noticed, and at 10 p. m. there was well-marked hyperpnea; she could scarcely be aroused; there was marked involuntary twitching of the facial muscles, and the carbon dioxide tension of the alveolar air was 20 mm.

The next day the symptoms remained unchanged. On the third day the conditions improved somewhat and by November

TABLE I

DATA FROM A CASE OF SEVERE DIABETES MELLITUS. THE SYMPTOMS OF ACIDOSIS WERE MOST MARKED AT THE BEGINNING OF THE MENSTRUAL PERIOD

Date	Urine						Alveolar CO <sub>2</sub> Mm. Hg.	NaHCO <sub>3</sub> by mouth Gm.	Food					Remarks
	Glucose	Reaction	Acetone bodies as B.-Oxybu- tyric ac. Gm.	N Gm.	NH Gm.	NH <sub>3</sub> Coefficient			Protein Gm.	Fat Gm.	Carbo- hydrate Gm.	Alcohol Gm.	Total calories	
9-23-17	36.5	Ac.	.....	7.74	2.14	22.9	23	96	4	0	4	33	During this period the patient was subjectively well; there was no hyperpnea, drowsiness or other symptom that might be referred to acidosis.	
9-24-17	+	Ft. ac.	.....	.....	.....	38	96	27	12	5	0	243		
9-25-17	28.1	Ac.	79.7	8.58	3.50	34.0	48	37	53	4	0	661		
9-26-17	24.3	Ac.	39.9	8.37	3.38	37.0	25	24	55	43	8	658		
9-27-17	Trace	Ac.	14.0	4.62	2.37	42.4	25	24	10	1	0	183		
9-28-17	0	Ac.	19.2	4.77	1.88	34.8	23	24	18	11	7	338		
9-29-17	1.2	Ac.	8.0	2.00	0.92	38.0	23	24	40	31	12	404		
9-30-17	Trace	Ft. alk.	.....	2.72	0.99	30.2	31	24	14	14	0	188		
In the interval the patient was kept on a diet varying between starvation and 1500 calories of carbohydrate-free food. The urine was never sugar-free, excepting as the result of starvation. The carbon dioxide tension of the alveolar air varied between 23 and 36 mm. of mercury. Except for the presence of acetone bodies in the urine, there were no further signs or symptoms of acidosis noted.														
10-28-18	24.8	Ac.	39.2	9.28	3.90	34.6	20	12	3	0	0	12	First day of menstrual period; marked hyperpnea, extremely drowsy, very restless at times, twitching of facial muscles.	
10-29-17	22.5	Ac.	56.4	13.73	2.03	12.2	25	88*	4	0	0	16	Hyperpnea, drowsy, nauseated.	
10-30-17	16.2	Ac.	43.3	12.73	3.93	25.4	29	56	12	7	0	114	Brighter; breathing normal; still very drowsy.	
10-31-17	25.4	Ft. alk.	49.0	12.00	4.50	31.0	36	48	39	31	7	478	Considerably brighter.	
11-1-17	17.7	Ac.	54.7	8.47	3.53	33.3	32	38	21	10	0	392	Normal.	
11-2-17	6.8	Ac.	22.3	5.54	2.83	42.0	16	13	1	0	39	336		
11-3-17	15.3	Ac.	29.7	8.04	3.15	32.3	16	45	35	12	0	509		
11-4-17	16.3	Ac.	34.4	8.09	4.02	41.0	16	15	1	0	39	344		
11-5-17	11.6	Ac.	32.9	6.75	2.76	33.8	16	15	1	0	39	344		
11-6-17	10.6	Ac.	24.5	7.36	3.07	34.5	16	15	1	0	39	344		
11-7-17	5.6	Ac.	16.9	4.92	1.96	32.9	16	15	1	0	39	344		
11-8-17	14.0	Ac.	28.4	16.89	3.09	15.1	16	71	72	12	39	1283		
11-9-17	9.8	Ft. alk.	24.4	7.12	2.93	34.0	16	52	65	12	39	1140		
11-10-17	8.9	Ac.	32.6	6.89	2.24	26.8	16	50	31	12	13	634		
11-11-17	7.3	Ac.	27.8	6.40	2.42	31.3	16	31	32	12	13	485		
11-12-17	17.1	Ac.	25.1	6.77	1.86	23.0	16	46	31	12	13	617		

\* Besides sodium bicarbonate by mouth, 25 gms. were given by intravenous injection and 30 gms. by rectum.

bonate of soda administered. The patient was thin and weak, but exhibited none of the distressing subjective symptoms that are often associated with marked acidosis and impending diabetic coma. The gravity of the situation was realized, and every effort was made to improve the girl's condition. At the end of one month, the acidosis had somewhat diminished, but the tolerance for carbohydrates had not increased at all. She was evidently one of the rare but unfortunate cases of diabetes mellitus which are not relieved by the starvation treatment.

1 all the symptoms which had manifested themselves at the time of menstruation began had disappeared. The patient was treated with large doses of bicarbonate of soda by mouth, rectum, and intravenously, and by starvation. The effects of this therapy were satisfactory.

The tests during this period, which may be regarded as one of diabetic coma, show no appreciable increase in the severity of the acidosis over that of one month previously when there were no subjective symptoms of acidosis. There is perhaps a slight tendency toward a rise in the amount of acid substances and ammonia, but no significant change occurred.

The alveolar air showed a lower tension of carbon dioxide on the first day of menstruation than had previously been recorded, but here again the difference was only slight. It may,

<sup>1</sup> Marriott, W. McK.: Jour. Am. Med. Assn., 1916, LXVI, 1594.

<sup>2</sup> Atwater and Bryant: U. S. Dept. of Agriculture, Bull. No. 28, 1906.



therefore, be concluded that the process of menstruation in some manner affected the body so that it was less resistant to the influences of the acid bodies and that diabetic coma resulted.

There are several other facts that point to the profound effects which were produced by the menstrual process. During the period the glycosuria and the quantity of nitrogen in the urine were both much increased. These phenomena have often been noted in so-called cases of acute diabetes. When menstruation had ceased, it was apparent that some permanent damage to the carbohydrate metabolism had occurred. The amounts of glucose excreted were somewhat higher than before, and the acidosis, as indicated by the acetoneuria and the quantity of ammonia in the urine, was distinctly more pronounced.

Letters received from the patient's mother and her physician would seem to show that during the two weeks after she left the hospital (November 11) her condition was thought

to be unchanged. She was permitted to be up and about and there was presumably very little restriction imposed upon her diet. On November 25 menstruation began. She was very drowsy and nauseated. Deep coma came on during the course of the day, and on the following day several general convulsions occurred. There was evidently typical air hunger. Death came about 36 hours after the onset of the diabetic coma, and on the third day following the beginning of the menstrual period.

In this case of diabetes mellitus it seems justified to conclude that the menstruation was accompanied by an increase in the acidosis. The symptoms became more marked with each successive period until fatal coma occurred. This is not a common sequence of events, but may possibly be regarded as an indication that diabetic patients should be closely observed during the menstrual period.

## A CASE OF COLLOID DEGENERATION OF THE SKIN WITH AN UNUSUAL HISTOLOGICAL FEATURE

By LLOYD W. KETRON, M. D.

(From the Dermatological Department of The Johns Hopkins University)

Colloid degeneration of the skin was first described in 1866 by Wagner, who gave it the misleading name of *colloid milium*. It is a very rare disease. According to Hartzell<sup>1</sup> only 22 cases have been recorded and in a relatively large number of these the correctness of the diagnosis is open to question. Arzt<sup>2</sup> claims that in only 10 of the reported cases was the diagnosis definitely confirmed by histological examination.

The following example of this disease is reported in order to put the case on record and also emphasize an unusual histological feature:

The patient was a Virginian, aged 42, single, and a carpenter by trade. He had had no serious illnesses and his general health had always been good. He chewed tobacco, but did not smoke nor use alcoholic drinks. In his work he was not in the habit of handling paints, oils or chemicals.

The disease had begun (as the patient described it) 12 years before, with the appearance of a "little patch of warts" on the back of the left hand just behind the knuckle of the forefinger. Very soon afterwards the back of the right hand had become affected, and the eruption had very gradually reached its present extent. The ear had been implicated for about five years. There had been no subjective symptoms.

On examination, the process was found to be limited to the backs of both hands and the helix of the left ear (Figs. 1, 2 and 3). It extended on to the first phalanges of some of the fingers, but the palmar surfaces were not involved. On the hands the eruption consisted of a thick aggregation of papillo-

matous lesions somewhat larger or smaller than a pinhead and with an elevation of 1 or 2 mm. They were round, oval or triangular in shape, and occasionally semiglobular ones with restricted bases were found. The surfaces of most of the lesions were smooth, flat, and frequently had a glazed appearance. In the center they were brownish- or reddish-yellow in color and appeared to contain fluid. One of them was pricked with a needle but no fluid escaped. The whole top was then pulled off and a jelly-like, friable, brownish-yellow substance was disclosed, embedded in the skin. It was easily expressed, leaving an opening which rapidly filled up with blood.

On the ear (Fig. 3) the disease extended along the helix, forming a protuberance about 3 cm. long and 3 or 4 mm. high. Here the lesions did not form separate elevations as on the hands, but a diffuse thickening with a more even surface was formed, within which could be seen the brownish or yellowish masses embedded in the skin.

No other dermatological condition was noted except a large number of black comedones over the nose, cheeks and forehead.

*Histological Examination.*—A piece of tissue was excised from the back of the hand and the sections stained with: (1) hematoxylin and eosin; (2) picric acid and fuchsin; (3, 4) Weigert's elastic tissue stain combined with (a) safranin and (b) hematoxylin; (5) acid orcein; (6) polychrome methylene-blue.

No change was noted in the epidermis except a flattening out of the interpapillary pegs.

In the papillary layer of the cutis, round or irregular masses of a homogeneous material were found, which had raised the epidermis up into the papular elevations noted in the clinical descriptions (Fig. 4). These masses were not confluent and were rather sharply separated from the surrounding colla-

<sup>1</sup> Colloid Degeneration of the Skin with Report of a Case of So-Called Colloid Milium. *The Journal of Cutaneous Diseases*, 1914, XXXII.

<sup>2</sup> Zur Kenntniss des "Pseudo-Milium colloidalis." *Arch. f. Dermat. u. Syph.*, 1914, CXVIII.

genous and elastic tissues. They were divided up into irregular blocks by branching lines which appeared as a simple break or consisted of one or more strands of connective tissue, in which were well-preserved nuclei and occasionally small blood-vessels (Fig. 5). (The fixation, staining and manipulation of the sections have resulted in a noticeable separation of many of the blocks.)

The most striking thing observed in the histological study were peculiar cells with round or oval vesicular nuclei, apparently embedded in the colloid blocks or lying along the connective-tissue strands between them (Fig. 5). They were comparatively scarce, but a few of them were found in all of the sections. They occurred singly or in groups and in one instance surrounded an opening in glandular fashion (Fig. 5, c). Their size varied from that of a small lymphocyte to that of one 4 or 5 times as large. The protoplasm, especially of the larger cells, was abundant and filled with granules which took the stains somewhat as did the colloid material, although much more faintly. These cells frequently appeared as if they had been carved out of the surrounding colloid material. Pseudopodia-like processes were occasionally present. Many of them, however, were not so striking in appearance and differed in no way from the connective-tissue cells except that there were a few granules in the protoplasm. Most of the cells apparently contained only one nucleus, but frequently they lay together in such a manner that their outlines were not well defined.

The elastic tissue in the upper half of the corium was partly swollen and degenerated and a narrow fringe lay between most of the colloid masses and the epidermis.

I was unable to follow the formation of the colloid from collagen, or to find the large amounts of collagen as described by Unna.<sup>3</sup> The lines of division between the collagenous and elastic tissues, on the one hand, and the colloid masses, on the other, were on the whole rather sharply defined.

No definite colloid changes were found in the blood-vessels of the corium, the sweat glands or epidermal cells.

Histopathology of The Diseases of The Skin (English translation), 1896.

The only unusual feature which the histological study has brought out are the peculiar cells which lay in the colloid masses. These have apparently been mentioned by only one investigator, Bizzozero.<sup>4</sup> Although he does not speak of the granular nature of the protoplasm, I presuppose them to be cells similar to those I have seen. He describes them as containing large vesicular single or multiple nuclei and a more or less distended (*geblätes*) rich protoplasm with narrow processes. The author believes that they originate from endothelial and connective-tissue cells.

I was especially interested in these cells because they reminded me of those described by Dr. Gilchrist and myself in a case of fatty atrophy of the skin.<sup>5</sup> (In this case, however, the granules were represented in the sections only by vacuoles, since the fixative agent had dissolved out the granular material.) We showed that these cells were macrophages which had taken up the fat probably because some chemical change had converted it into a foreign body.

I believe the process is similar in the case of colloid degeneration of the skin, and that these peculiar cells are macrophages or cells which have phagocytosed the colloid material in an attempt to remove it from the tissues. The cells of this type are usually derived from connective-tissue and endothelial cells. In our case, they have most likely been formed from the well-preserved connective-tissue cells which were present in the colloid masses.

*Conclusions.*—A typical case has been reported of the rare condition of colloid degeneration of the skin. In the histological study, peculiar cells with granular protoplasm were found embedded in the colloid blocks. These have apparently been described by Bizzozero, but he did not recognize their nature or function, if my conception of them is true. I believe them to be macrophages which have phagocytosed the colloid material, because of its foreign body reaction.

I wish to thank Dr. Gilchrist for permission to publish this case.

<sup>4</sup> Ueber eine klinisch ganz eigenartige Form von Pseudo-Colloid-millium. Arch. f. Dermat. u. Syph., 1910, XCV.

<sup>5</sup> A Unique Case of Fatty Atrophy of the Skin, etc. THE JOHNS HOPKINS HOSPITAL BULLETIN, 1916, XXVII.

## A SARCOMA OF THE UTERUS ARISING FROM THE ENDOMETRIUM

By LEO BRADY, M. D.

(From the Gynecological Department of The Johns Hopkins Hospital)

GYN. No. 33231. S. F., aged 53, entered The Johns Hopkins Hospital, on Dr. Cullen's service, July 23, 1917, complaining of slight uterine bleeding and of a small lump in her left breast. The breast condition gave the patient more concern than did the bleeding.

Her family and previous histories were negative. The patient had been married 31 years and had had three children. These were living and well. The labors were spontaneous and not difficult, and there was no later trouble. The patient had

ceased menstruating several years before, but for the last six months had been having some bloody discharge from the uterus. This was very scanty in amount. When she entered the hospital her chief complaint was of a small lump in the left breast, which she had noted for some time.

On pelvic examination the outlet was found to be moderately relaxed, the cervix normal in consistency, not enlarged. The uterus was about twice the natural size, regular in outline and freely movable. No pelvic tenderness was made out.

*Operation.*—On July 25, 1917, Dr. Cullen dilated and curetted the uterus and obtained a considerable amount of material. While frozen sections of the curettings were being made the breast nodule was examined. This nodule was about 1.5 cm. in diameter. It was removed and was found to be a simple cyst. By this time the scrapings had been examined. The frozen sections showed the typical picture of a round-cell sarcoma.

The cervix was then sewed up to prevent any of the sarcomatous material from escaping during the abdominal operation. The entire uterus and both tubes and ovaries were removed.

On the day following operation, the patient was in good condition, but on the afternoon of the second day her temperature ran up to 104° F. Her general condition, however, was good and there was no abdominal distention. On the third day she was in good condition, but on the fourth day her temperature rose to 105° F. As the patient came from Canada and from a location where one would not suspect malaria this was not at first thought of, but it was learned that she had just been visiting some friends along the Potomac. Examination of the blood showed both sexual and asexual forms of the malarial parasites. Under quinine therapy the infection cleared up and on August 17 the patient was discharged in excellent condition. She was heard from again on November 1, 1917, when she wrote that she had no symptoms in any way suggesting a recurrence of the growth.

*Gyn. Path. No. 23234.*—The specimen consists of a uterus with both tubes and ovaries attached, the entire mass weighing 140 grams. The uterine cavity measures 8 cm. in length. When the uterine cavity was opened, there was seen a heart-shaped growth attached to the upper part of the fundus near the left cornu. The growth measured 4 x 5 x 4 cm. and felt quite soft. In fresh section the cut surface was homogeneous; the color white, mottled, with light yellow. Several large venous sinuses stood out plainly. The uterine mucosa seemed normal everywhere except at the point where the tumor had arisen. The tubes and ovaries and cervix were perfectly normal and careful measurements showed them not to be enlarged. There were no adhesions around the uterus, tubes or ovaries.

Fig. 1 shows very clearly the heart-shaped growth arising from the endometrium near the base of the fundus; the rest of the endometrium and the tubes and ovaries appear to be normal. Sections taken from the cervix, tubes and ovaries show no invasion of these tissues by the growth.

The microphotographs (Figs. 2, 3 and 4) are from frozen sections through the growth and uterus at the place of attachment of the growth and fundus.

At the top of Fig. 2 the letter *b* denotes the uterine muscle, which shows no signs of myomatous change. Below this we have a region (*a*) in which we find remains of the uterine glands. At the bottom of the picture we have only tumor cells.

Fig. 3 shows the tumor cells invading the muscle tissue. It is to be noted here, also, that even at the point where the tumor and muscle tissue come together there are no myomatous changes. At *a* is an island of tumor cells surrounded by normal uterine muscle (*b*).

Fig. 4 shows a high-power field taken from the sarcoma itself and demonstrates the extremely cellular character of the growth and the masses of deeply staining cells.

This case is interesting principally because it is an example of the importance of paying attention to any menstrual irregularity in women of the cancerous age. Here we have a woman entering the hospital worried because of a lump in her breast which turns out to be, on operation, a benign tumor, but paying little attention to the recurrence of vaginal bleeding, one and a half years after the menopause, which scrapings demonstrated to be due to a very malignant growth.

Finally, the case is interesting because we are apparently dealing, not with a sarcoma starting from a malignant degeneration of a fibroma, as is usually the case, but with one arising from the connective tissue of the endometrium. Certainly we find no myomatous changes anywhere, and on examining the sections one cannot help but be struck by the fact that the tumor cells have arisen from the region where we find the remains of the uterine glands. Such tumors, while occasionally reported, are nevertheless quite rare.

I wish to extend my thanks to Mr. Max Brödel and to his pupil, Miss Ethel Norris, who made the excellent drawings of this tumor.

## A PHARMACOLOGICAL APPRECIATION OF SHAKESPEARE'S HAMLET: ON INSTILLATION OF POISONS INTO THE EAR

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Shakespeare's works abound in references to drugs and poisons; some of these pertain to the mystic vagaries and superstitions of kakopharmacy or dirt medicine, alchemy and witchcraft; others, on the other hand, are borrowed from the more scientific, even though empirical, data furnished by the materia

medica and poison-lore of antiquity and the Middle Ages. In the present paper I have attempted to analyze and discuss in the light of modern science a passage in Hamlet which is of extreme interest to the student of medical history from the pharmacological and toxicological points of view. I am refer-



ring to the manner of Hamlet's father's death as described by his ghost in Act I, Scene 5, lines 59 to 73. The passage in full reads as follows:

"Sleeping within mine orchard,  
My custom always in the afternoon,  
Upon my secure hour thy uncle stole,  
With juice of cursed hebenon in a vial,  
And in the porches of mine ears did pour  
The leperous distilment; whose effect  
Holds such an enmity with blood of man  
That swift as quicksilver it courses through  
The natural gates and alleys of the body;  
And with a sudden vigour it doth posset  
And curd, like eager droppings into milk,  
The thin and wholesome blood: so did it mine;  
And a most instant tetter bark'd about,  
Most lazar-like, with vile and loathsome crust  
All my smooth body."

The points of interest to us as medical men in connection with these lines are: Firstly, what is meant by the poisonous hebenon, or hebona as it appears in some editions? Secondly, what were the properties of that poison as known to Shakespeare? Thirdly, what do we know of the poison in the light of modern toxicology? Fourthly, how common was the method of instillation of poisons into the ear in ancient and medieval times? And lastly, what does modern pharmacology teach us as to the possibility of absorption of drugs and poisons through the intact ear? I may say at once that all of the above points with the exception of the last have been more or less discussed by Shakespearean scholars. I have, however, not been able, even after a most laborious search through the literature, to find any information as to the possibility of absorption of poisons through the intact ear. This fact has led me, in connection with this historical research, to undertake an experimental investigation on the subject, especially as I have during the past year been engaged in the study of absorption of pharmacological reagents through devious and unexpected channels, the results of which have partly already been published.

#### VARIATIONS IN READINGS

Two different readings for the poisonous plant employed by Hamlet's uncle in the murder are found in different editions of the play. In the first edition of Hamlet, the Quarto of 1603 ( $Q_1$ ), we find:

"With juyce of Hebona  
In a viall."

In the Quarto of 1604 ( $Q_2$ ) and in all the subsequent quartos ( $Q_3$ ,  $Q_4$ ,  $Q_5$  and  $Q_6$ ) the reading is also Hebona, as follows:

"With juyce of cursed Hebona in a viall."

In the Folio of 1623 ( $F_1$ ) and in subsequent folios, on the other hand, the reading is hebenon, as quoted above, and this reading is followed by all subsequent editions of Hamlet. It is thus seen that two different words, *hebona* and *hebenon* are employed for the poisonous plant used by the murderer. What these words mean, whether the two words are but different terms for the same plant or whether the two refer to two different kinds of poisons and what these poisons were, has been

a bone of contention among Shakespearean students for many years.

#### HEBONA OR HEBENON

Various explanations of these words are given by different scholars. I have found altogether five interpretations: some holding that hebona or hebenon means the yew-tree; others that it refers to henbane or *hyoscyamus niger*; still others explain it as *ebony*; a few suggest that the word may refer to hemlock; and a few others think that the deadly nightshade or belladonna is here meant.

Thus Grey<sup>1</sup> says, "Hebenon stands by metathesis, for hebenon, that is, henbane, of which the most common kind, *hyoscyamus niger* is certainly narcotic, and perhaps, if taken in considerable quantity, might prove poisonous." Singer<sup>2</sup> says: "The French word *hebenin* applied to anything made from ebony comes indeed very close to the hebenon of Shakespeare." Elze<sup>3</sup> suggests: "Perhaps should we not conjecture that hemlock was intended here?" Beisley<sup>4</sup> states, on what grounds it is not clear, that "Hebenon might have been originally written *eneron*, one of the names common at that time for *solanum maniacum*, called also the deadly nightshade." Tschischwitz<sup>5</sup> says: "Hebona can be only a mistaken substitution of the Spanish and Italian *ebano*, the French *ébène* and the Latin *ebenus* and *hebenus*, all of which mean ebony." Nicholson<sup>6</sup> and Harrison,<sup>7</sup> on the other hand, both of whom are profound Shakespearean scholars, adduce some very good evidence that hebona is the original reading and that it refers to the yew-tree, well known to the ancients for its poisonous properties. A review of all the evidence on the subject leaves only two explanations of the word worthy of consideration: that of hebona, meaning the yew-tree, and that of hebenon as a corruption of the word henbane.

#### CONCERNING HEBEN, THE YEW-TREE

There is a great deal of evidence in favor of the hebona of the quarto texts of Hamlet as having reference to the English yew-tree or *taxus baccata*. Though the form hebona is somewhat unusual, the word *hebon* is not uncommon among other Elizabethan writers. Thus in Marlowe's Jew of Malta, Act III, Scene 4, we find:

... "The blood of Hydra, Lerna's bane  
The Juice of Hebon, and Cocytus' breath."

where hebon is generally taken for *heben*, the yew-tree, branches of which were much used by archers in old England for making their bows. In Spenser's Faerie Queene, we find the following verses:

"Lay now thy deadly Heben bow apart" (I, Pr. 3, 5).  
"His speare of heben wood behind him bare" (I, vii, 37, 2).  
"Trees of bitter gall and Heben sad" (II, vii, 52, 2).  
"Heben lance and covered shield" (II, viii, 19, 6).

The yew-tree, *taxus baccata*, has borne the reputation of being poisonous from remote antiquity. Dioscorides, speaking of the juice of green yew leaves, writes that it speedily produces death.<sup>8</sup> Pliny speaks of it as "*taxus tristis et dira*,"<sup>9</sup> and adds that drinking-cups made from this tree were found

to impart a deadly property to the wines drunk out of them. Statius,<sup>10</sup> Lucretius<sup>11</sup> and Plutarch,<sup>12</sup> all describe the taxus or yew-tree as being poisonous. "Metuendaque succo taxus," says the first of these; "the juice of the yew is to be feared." Nicholson indeed points out that Shakespeare's expression, "cursed hebona" and "holds such enmity with blood of man," may have been suggested by Pliny's description of the plant. Spenser's epithet of "deadly" applied to the heben bow must also refer to the poisonous properties of the yew. Shakespeare himself mentions the yew-tree four times in his plays and in every case connects it with death or some sad event. Thus in Twelfth Night, Act II, Scene 4, line 55, we read:

"My shroud of white, stuck all with yew,  
O prepare it."

In Titus Andronicus, Act II, Scene 3, line 107, we read:

"But straight they told me they would bind me here,  
Unto the body of a dismal yew."

In Macbeth, Act IV, Scene 1, line 27, the witches howl:

"Slippes of yew  
Silvered in the moon's eclipse."

And in Richard II, Act III, Scene 2, line 113, we find:

"Learn to bend their bows  
Of double fatal yew."

The expression "double fatal" in the last quotation refers evidently to the poisonous properties of the yew in addition to its being a weapon of warfare. All the citations given above certainly point to the prevalence of the belief in Shakespeare's times that the yew-tree was poisonous and may have well suggested to him its use in the play. Let us now inquire into what modern toxicology can tell us concerning the properties of *taxus baccata*.

#### ON THE TOXICOLOGY OF TAXUS BACCATA

If we examine scientifically the literature on the subject of yew poisoning we shall be surprised to find abundant evidence as to the poisonous nature of the plant. Not only the berries but also, and to a greater degree, the leaves and the bark of *taxus baccata* have proved poisonous. The ancient authorities on the subject have already been cited; a considerable number of cases of poisoning are described by modern writers. Thus Falk<sup>13</sup> has collected 32 cases of poisoning by *taxus baccata*, nine of which resulted from eating of the red berries and 23 from the swallowing of infusions of the leaves. Twenty of the patients died, making the percentage of fatal cases 62½ per cent. Hurt<sup>14</sup> reported the death of a child of three and a half years who swallowed a quantity of yew berries. New<sup>15</sup> reported a case of poisoning in an insane patient who swallowed a large quantity of them. Taylor<sup>16</sup> reports two cases of severe yew poisoning. Heffter<sup>17</sup> describes a fatal case of poisoning in an adult; and other cases may be found cited in the toxicological reference works by Kobert,<sup>18</sup> Kunkel<sup>19</sup> and Blyth.<sup>20</sup>

The leaves of the yew were not infrequently employed to induce abortion.

The chemistry of *taxus baccata* has been studied by the French toxicologist Marmé,<sup>21</sup> who isolated an active principle

with alkaloidal properties which he named *taxin*. This is an amorphous white powder having the empirical formula  $C_{27}H_{32}NO_{10}$ , soluble in alcohol, ether and chloroform, insoluble in benzene and slightly soluble in water. The substance melts at 82°C. and gives an intense purple-red color with  $H_2SO_4$  and a reddish-violet color with Froehde's reagent. The salts of taxin are freely soluble in water. Lewin<sup>22</sup> gives the lethal dose of taxin for frogs as being from 50 to 70 mgms., and for cats as being from 30 to 50 mgms. The lethal dose for man is not given, but death has been reported to occur rapidly after swallowing large quantities of the infusion from leaves in from one and a half to twenty-four hours. The chief experimental work on yew poisoning has been done by Borchers,<sup>23</sup> who found that death was produced primarily through respiratory paralysis. Taxin, however, was found by him also to be poisonous to the heart and to the central nervous system. Concerning the pathological findings in fatal cases, there is nothing characteristic reported by reliable pathologists, the only constant lesion being an intense inflammation of the intestines.

#### ON THE RELATION OF THE WORD HEBEN TO EBONY

Mention has already been made of the hypothesis advanced by some Shakespearean students that hebona might really refer to the ebony tree. It therefore behooves us to inquire whether the ebony tree or *diospyros ebenus* of India is poisonous or not. There is no evidence in the literature ascribing to the ebony tree any poisonous properties. Among modern authorities the most complete account of the medicinal properties of the ebony tree is by W. Ainslie.<sup>24</sup> This writer states that the juice of the ebony is perfectly innocuous, and that it is used by the natives as a remedy for certain complaints of the liver and in cases of dysentery. Shakespeare, therefore, could hardly have used the word *hebona* to mean the ebony tree.

The confusion of hebona with ebony, however, is interesting from the etymological point of view. The English word heben, yew-tree, is really the same word as ebony applied to the *Diospyros ebenus*. The Greek ἔβενος, the Latin ebenus, the Italian and Spanish ebano and the French ébène, all names for ebony, all come from the original Hebrew root *eben*, which means a stone, and refer to the hardness of ebony wood and not, as may be at first glance supposed, to its color. Nicholson and Harrison call attention to the fact that in the Middle Ages the word ebenus or ebony was applied to any hard wood, and thus it came to pass that the same term was used to mean also the yew-tree, the wood of which is remarkable for its hardness. Thus arose the Scandinavian and high and low German words *Eben*, the Dutch *Iben*, the Swedish *Eben*, the modern German *Eibe(n)* and the Danish *Heben*, a form which is also found in Elizabethan literature.

#### CONCERNING HEBENON AND HENBANE

Whereas the advocates of the yew-tree theory regard the reading *hebenon* of the Folios as a misprint for the earlier *hebona*, another set of critics hold the view that *hebenon* is the correct reading and that it is a synonym of the well-known

henbane. There is a good deal of sound evidence that can be adduced in favor of this view. In the first place, metathesis of consonants is not at all an unusual phonetic phenomenon. Secondly, the argument advanced by some that hebenon is spelled with an "o" while henbane has an "a," is not a valid one because, according to Hanbury and Flückiger,<sup>23</sup> the writing *hennibone* for henbane is found in a vocabulary of the thirteenth century. Thirdly, the poisonous properties of hyoscyamus or henbane were known from the remotest antiquity and, furthermore, henbane was a common drug in Shakespeare's time. Fourthly, the poisonous properties of henbane are not infrequently mentioned in old English literature. Thus, Drayton in his *Barons' Wars*, p. 51, speaks of

"The poisoning henbane and the mandrake dread."

And again

"Here Henbane, Poppy, Hemlock here  
Procuring deadly sleeping."

Again in *The Philosopher's Fourth Satire of Mars* by Anton (1616), we find the following verse:

"The poison'd henbane whose cold juice doth kill."

Fifthly, henbane is an official drug mentioned in old English pharmacopeias and dispensaries such as those by Dale and Salmon and others, and has been used from ancient times in the form of *ear drops*. Lastly, but not least in importance, and indeed of great significance, is the fact that Pliny describes toxic symptoms following instillation of henbane oil into the ear.

"Oleum fit ex semine quod ipsum auribus infusum temptat mentem."<sup>1</sup>

Which means that the oil of hyoscyamus seeds instilled into the ears produces madness. It is to be noted that the very popular English translation of Pliny by Holland appeared in 1600. Inasmuch as the first quarto edition of *Hamlet* was probably written in 1600, though not published until 1603, Shakespeare undoubtedly must have been familiar with Holland's work and very probably might have had it in mind in issuing the later editions, and for that reason might have changed the reading of hebona to hebenon.

#### ON THE TOXICOLOGY OF HYOSCYAMUS

The poisonous properties of hyoscyamus or henbane are too well known to be given here in detail. Henbane is certainly just as poisonous and in fact more poisonous than the yew-tree. Cases of poisoning with hyoscyamus are not at all uncommon and are described in the literature, ancient, medieval and modern. Detailed descriptions of such cases may be found in Blyth, Kobert, Kunkel, Peterson and Haines<sup>24</sup> and other text-books on toxicology. It is well to bear in mind, furthermore, that while *hyoscyamin*, the lethal dose of which is a little over one grain, is the principal constituent of hyoscyamus niger, the crude plant also contains variable quantities of the even more powerful alkaloids, *atropin* and *scopolin*.

The minimal lethal doses of hyoscin are even less than that of hyoscyamin. A strong extract of hyoscyamus would therefore be a very powerful poison.

#### DISCUSSION

Whether hebona or yew-tree, or whether hebenon or henbane, is the correct reading in the passage before us will probably be never settled, nor will we venture to assert an opinion as to which drug or poison Shakespeare meant. Indeed, for the appreciation of *Hamlet* either reading may be chosen. As a pharmacologist, however, I cannot help surmising that both hebona and hebenon might have been written by Shakespeare himself. It would not be too far-fetched to suppose that the idea of a powerful poison was suggested to the author by the yew-tree on the one hand, while the unusual administration of it through the ears was suggested by henbane, on the other. Certainly the practice of instilling hyoscyamus into the ear was not unknown in Shakespeare's times, and the appearance of Holland's translation of Pliny just about the date of the first quarto edition of *Hamlet* lends further support to this view.

Much has been made of, by older writers, of Shakespeare's description of the effects of the poison as an argument for and against the yew or the henbane theory by the respective critics on the one side or the other. These arguments are amusing to the modern toxicologist, as we cannot say that the symptoms pictured in the passage before us are more applicable to the one poison than the other. Nor have we a right to expect the author to have known the detailed symptomatology produced by either. Three features are mentioned in connection with the hebona or hebenon poisoning which we are discussing. Firstly, Shakespeare speaks of the rapidity of the toxic effect:

"Swift as quicksilver it courses through  
The natural gates and alleys of the body."

Secondly, reference is made to peculiar leprosy-like cutaneous manifestations of the poisonous effect:

"A most instant tetter barck'd about  
Most lazarus-like, with vile and loathsome crust  
All my smooth body."

Thirdly, mention is made as to the circulatory effect:

"With a sudden vigour it doth posset  
And curd, like eager droppings into milk,  
The thin and wholesome blood."

It cannot be said that the yew-poisoning runs a more rapid course than that following hyoscyamus. Both are rapid in their action. Harrison quotes an old French writer as stating that the yew-tree gives rise to a characteristic cutaneous eruption and uses this point as a strong argument in favor of hebona, the yew. None of the modern authorities, however, describe any specific cutaneous lesions in connection with poisoning by *taxus baccata*. In fact, skin eruptions result perhaps more commonly after the giving of hyoscyamus and belladonna even in non-lethal doses. Lewin<sup>25</sup> describes erythema, urticaria, pustules, and even purpura occurring in sensitive persons after therapeutic doses of hyoscyamus preparations. Nor does modern toxicology and pharmacology show any specific

<sup>1</sup> Natural History, XXV, 17.



effect of toxin or hyoscyamin on the blood corpuscles or the plasma, so that Shakespeare's simile must be taken merely as a forcible poetic description of the rapid paralysis of respiration and circulation produced by the poison used.

#### ON THE INSTILLATION OF POISONS INTO THE EAR

The method of poisoning described in connection with the murder of Hamlet's father is unique and unusual. Although drugs were used in treatment of ear affections in ancient times, no reference is found of their instillation into the ears for homicidal purposes. The doubtful credit for such *finesse* in the administration of poisons must be ascribed to medieval experts and more particularly to the Italians and French. A character in one of the old plays says "Poison speaks Italian." It is well known that poisoning rose to the distinction of an art at that time in Italy and France. A perusal of fascinating books dealing with professional poisoning in the Middle Ages, such as those by Legué<sup>22</sup> or by Thompson<sup>23</sup> and others, will furnish astounding corroboration of this fact. One of the famous older works dealing with the art of poisoning is the *Magia Naturalis* or *Natural Magic* of the Italian de la Porta. This writer discusses various subjects, and in a chapter on cookery gives some delicious recipes for demoniacal concoctions calculated to produce unflinching results. The following example from de la Porta, quoted by Thompson, will serve as a good illustration of some of the poisonous concoctions used in his times.

#### VENENUM LUPINUM

"Take of powdered leaves of aconitum lycoctonum, taxus baccata, with powdered glass, caustic lime, sulphide of arsenic and bitter almonds; mix them with honey and make into pills the size of a hazelnut."

That such experts in the art of poisoning should have thought of instilling poisons into the ear is therefore not surprising. We find several references to such a procedure in old English literature. The following is a quotation from Marlowe's *Edward II*, Act V, Scene 4:

"I learned in Naples how to poison flowers;  
To strangle with a lawn thrust down the throat;  
To pierce the windpipe with a needle's point;  
Or whilst one is asleep, to take a quill  
And blow a little powder in his ears:  
Or ope his mouth and pour quicksilver down."

Another reference to poisoning through the ears is found in a later passage in *Hamlet*, Act III, Scene 2, in connection with the re-enactment of the murder by the players under the direction of Hamlet. Here we read:

"His name's Gonzago; the story is extant, and writ in choice Italian."

A note in the Arden edition of *Hamlet* in connection with this passage says:

"In 1538 the Duke of Urbino married to a Gonzaga, was murdered by Luigi Gonzago, who dropped poison into his ear."

One other case of poisoning through the ears, of especial interest to us as medical men, is mentioned by Robert<sup>24</sup> in his thesis on the Poisonings of the Middle Ages. It is well known that King Francis II of France died very suddenly; his death was supposed to have been due to poisoning, and the celebrated French surgeon, Ambroise Paré, was deliberately accused, of course without foundation, of having murdered the king by blowing a poisonous powder in his ear.

It is very interesting to note that the original Hamlet story has no mention of instillation of poison into the ear.<sup>25</sup> In the Hamlet story by Saxo Grammaticus, Hamlet's father is killed by his brother with a steel weapon. The instillation idea is original with Shakespeare and was probably suggested by the prevalence of the horrible form of homicide by poisons so common at the time and the toxic properties of the yew-tree and henbane which we have already discussed in detail.

#### ON THE ABSORPTION OF DRUGS AND POISONS THROUGH THE INTACT EAR

In connection with Shakespeare's passage which we have just discussed in detail, an interesting scientific question arises as to whether drugs or poisons can be absorbed through the intact external ear canal and drum into the general circulation and produce constitutional symptoms. During the past year the author has been engaged in the study of absorption of drugs and poisons through unusual and unexpected channels, such as the eye,<sup>26</sup> the bladder, the urethra, the ureters, pelvis of the kidneys,<sup>27</sup> vagina,<sup>28</sup> etc. It was interesting, therefore, to inquire into and investigate experimentally the possibility of absorption of drugs through the ear. The results of these experiments will be published in detail in the *Journal of Pharmacology and Experimental Therapeutics*. It may be here stated that the author has found that a number of poisons can be and are absorbed through the intact ear.

The powerful alkaloid, aconitin, in the form of the hydrochloride, was found to be absorbed through the intact ears of animals even when introduced in an aqueous solution. Fig. 1 shows the characteristic effects of aconitin poisoning in a cat.

Equally rapidly and easily is absorbed through the ear the powerful volatile alkaloid nicotine. Fig. 2 illustrates the toxic action of this drug.

The question of absorption of belladonna and atropin was undertaken with especial interest in connection with Shakespeare's reference to henbane. It was found that atropin in an aqueous solution is not absorbed through the ear, but an alcoholic solution of the belladonna alkaloids in the form of a weak tincture gave positive experimental proof of the absorption of that drug as shown by the paralysis of the vagus terminals in the heart.

It is well known that a large number of drugs are introduced by physicians into the ears for medicinal purposes. Hyoscyamus in the form of an oil or a tincture has been long employed for the relief of earache; a compound tincture of hyoscyamus under the name of *Balsamum tranquillans* is official in several European pharmacopeias. In the light of

the experimental investigations just reported, such a use of hyoscyamus as an anodyne would certainly seem to be rational.

Another drug used in the treatment of ear affections with an intact drum is phenol or carbolic acid. A specialist tells me that he prescribes often in cases of middle-ear inflammation a few drops of a 5 per cent solution of carbolic acid in glycerin. I have found in experimenting on animals that such a solution of phenol in glycerin is absorbed through the ear, as evidenced by its effects on blood pressure. The use of carbolic acid in the treatment of ear affections, therefore, is on the one hand a rational one but on the other hand somewhat dangerous.

We cannot in this historical paper enter into a detailed account of the above experiments; they will be published in their proper place. Suffice it, however, to say that a number of drugs, and among them hyoscyamus or henbane, can be and are absorbed through the intact ear, and we may therefore conclude our appreciation of Shakespeare's passage from Hamlet which we have just been discussing, with saying that after all "Shakespeare was certainly right."

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## ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin  
Prepared by the Authors

### DUODENO-URETERAL FISTULA OF SPONTANEOUS ORIGIN

#### Report of Case

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(Abstract from the *Journal A. M. A.*, 1918, LXX, 276)

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital)

The proximity of the duodenum to the right renal pelvis, and the danger of injury to the former during nephrectomy, have been pointed out by Dr. W. J. Mayo, who cites four cases of duodenal fistula following nephrectomy, the first three of which were fatal, the fourth being cured by transperitoneal closure of the duodenum. The case reported herewith is doubly interesting in that it further emphasizes this danger of duodenal injury during nephrectomy, and presents a most unusual (and apparently unique) condition, namely, a definite demonstrable fistula connecting duodenum and ureter, which existed before any operative procedure had been carried out.

The patient was a man of 29, complaining of extreme frequency of urination, urgency and bladder irritability; and giving a history of an obscure fever, associated with pain in the right flank, occurring four years before admission. It is possible that this was a perinephritic abscess.

The general physical examination was negative. The urine showed large numbers of pus cells, bacilli and cocci.

Ureteral catheterization, repeated twice at weekly intervals, showed normal urine from the left kidney, and from the right, came scanty amounts of cloudy fluid, distinctly green in color, the sediment from which was made up largely of an amorphous mucoid material, containing a few pus and epithelial cells, and an occasional bacillus. There was no urea content, and not a trace of phenolsulphonphthalein. The resemblance of this greenish fluid to bile was mentioned at the time, but this possibility was not seriously considered, nor were tests for bile carried out. The phenolsulphonphthalein output from the left side, during one-half hour, was 30 per cent. It was quite evident, therefore, that the right kidney was functionally dead.

The pyelogram (right) showed no gross abnormality of the pelvis. At the level of the upper border of the third lumbar vertebra, and at about the uretero-pelvic junction, there was visible a small nipple or diverticulum of thorium, projecting from the ureter for about 1 cm. in a direction that seemed to be upward, outward and backward, and apparently ending blindly. This suggested an incompletely filled bifid ureter.

Nephrectomy demonstrated a duodeno-ureteral fistula. After dense adhesions around the kidney had been freed, and the latter delivered, it was noted that a knuckle of duodenum

was pulled up, and was intimately associated with the mass of scar tissue which included ureter, pelvis and pedicle in an indistinguishable mass. In dissecting the duodenum free it was necessary to cut into the ureter and leave a small area of the wall of the latter attached to the duodenum. Since the opening was very small and surrounded by scar tissue, and since the patient's condition was not good, no attempt at duodenal closure was made.

Convalescence was uneventful excepting that there was discharge of duodenal content from the incision from the fourth to the twelfth day. The most striking feature was the immediate cessation of bladder symptoms. On the day following the operation the patient began voiding without pain and at normal intervals, for the first time in two and one-half years; a remarkable contrast to the extreme bladder irritability before operation.

A careful study of the literature fails to reveal any other case of duodeno-ureteral fistula. In addition to the cases of duodenal fistula following nephrectomy reported by Mayo, there is a somewhat similar case of Thévenard in which a duodenal fistula developed 10 years after nephrectomy in a persistent sinus, probably tuberculous, which had existed since nephrectomy, with intermittent abscess formation. Van Vranken has reported a case, in a man, aged 45, with a large abscess of obscure etiology, pointing over the left Poupart's ligament, which he drained, finding that the abscess cavity communicated with the descending colon. After a month of fecal drainage from the abscess cavity, urinary drainage also appeared and persisted for several weeks, the fistula finally healing completely, although the case was followed for only six months. This case, in which colon and ureter discharged into a common abscess cavity, is the only one to be found in the literature which is in any way analogous to the case reported above.

In view of the history of intermittent attacks of chills and fever, accompanied by pain in the right flank; of the evidence found at operation of an old inflammatory process involving the perirenal tissues; and, of the fact that the duodenum, excepting at one point, was normal in appearance and consistency, the most plausible explanation of the origin of the duodeno-ureteral fistula is that the latter was preceded by a perinephritic abscess, which went on to spontaneous cure by rupture into both duodenum and ureter. The condition cannot be explained as an embryologic defect on account of the diverse origins of duodenum and ureter, the former arising from entoderm, and the latter being an evagination from the Wolffian duct, which is derived from mesoderm. It was fortunate that during the operation a good exposure was obtained, because the knuckle of soft-walled duodenum, when pulled up alongside the dense scar tissue at the hilum, could not be palpated, and was discovered only by inspection. It might readily have been clamped and severed with the pedicle, particularly if the necessity for hastily controlling hemorrhage through an inadequate incision had arisen.

The most interesting feature was the immediate cessation of bladder symptoms on the day after operation; the over-night

return to normal of a bladder which for two and a half years had been a constant source of distress. The only reasonable explanation is that the irritability was due to the constant presence of small amounts of duodenal content, and presumable trypsin, in the bladder.

*Conclusions.*—1. This case of duodeno-ureteral fistula is apparently unique.

2. In cases in which there is marked inflammatory reaction around the renal pedicle, the only safe procedure is to locate the duodenum before applying clamps.

#### URINARY ANTISEPSIS

##### A Study of the Antiseptic Properties and the Renal Excretion of Compounds related to Phenolsulphonphthalein: Preliminary Report

By EDWIN G. DAVIS, M.D.

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(Abstract from the Journal A. M. A., 1918, LXX, 581)

(From the James Buchanan Brady Urological Institute)

The ideal internal urinary antiseptic must be a drug which is chemically stable, non-toxic and non-irritating to the urinary tract; which is antiseptic in high dilution (in urine, as well as in water) and which is eliminated unchanged in high percentage by the kidney. There is no such drug known. A consideration of the properties possessed by phenolsulphonphthalein, however, shows that this compound comes very close to filling all the above requirements. Phenolsulphonphthalein is chemically stable, non-toxic and non-irritating, and is eliminated by the kidney with almost incredible rapidity and completeness; but it has no antiseptic properties, excepting in water in its free acid form. (Clinically, it is used as the monosodium salt.) In view of these remarkable properties, it was thought worth while to attempt a modification of the phenolsulphonphthalein molecule, with the hope that an antiseptic compound might be produced which still retained the desirable qualities of the original drug. As the problem gradually increased in scope, it was found advisable to investigate a large number of compounds distantly related to phenolsulphonphthalein, as well as those closely related. The total number of compounds experimented with is at present about 195, the antiseptic properties of which will be enumerated in subsequent publications. This report includes only those drugs closely related to phenolsulphonphthalein.

Each compound was investigated with two objects in view; first, to determine the rate of elimination by the kidney, and second, to determine the antiseptic properties. Rabbits were used for determining renal elimination, the drug being injected intravenously (in 10 mg. amounts, in 1 per cent solution), the animals catheterized after one hour, and a colorimetric estimation of percentage of excretion made with the Hellige colorimeter.

It was necessary to carry on parallel antiseptic tests for each compound both in urine and water. As will be shown below, and in subsequent publications, there are numerous compounds which are germicidal in high dilution in water, but which lose this property entirely when diluted in urine, and



which even permit the growth of organisms in urine when in relatively strong concentration. This astonishing fact has proved to be a great obstacle, for antiseptics in urine becomes, therefore, quite a different problem from antiseptics in water.

The metallic salts of phenolsulphonphthalein (Na, Ag, Cu, Hg and Ba) were all discarded because they were either toxic to the animals or inert as antiseptics in urine.

Of the sulphonphthaleins listed in Table I, the only one to show antiseptic properties in urine (pyrocatechinsulphonphthalein) fails to be excreted. It will be noted that there are several other sulphonphthaleins which show the same marvelous "renal affinity" as does phenolsulphonphthalein.

Of the halogen derivatives of sulphonphthaleins investigated (tetrabromphenolsulphonphthalein, tetrachlorphenolsulphonphthalein, di-iodophenolsulphonphthalein, dibromrescinsulphonphthalein and di-bromthymolsulphonphthalein), all are inert in urine, and none but the tetrachlor compound is excreted.

The phthaleins (phenolphthalein, thymolphthalein, tetrabromtetrachlorphenolphthalein, tetra-iodophenolphthalein, phenoltetrachlorphthalein and sulphonated phenolphthalein) are likewise useless. The last-named compound is excreted, although its chemical structure is quite different from that of phenolsulphonphthalein.

The xanthenes are characterized by the fact that two of the phenol groups are linked together by an oxygen atom, and they differ from the phthaleins only in this respect. Of the compounds of this class investigated (resorcinnaphthalein, resorcinsulphonphthalein, orcinsulphonphthalein, rhodamin and resorcinsaccharcin), all, in solution, are greenish and extremely fluorescent, and without exception they are excreted by the kidney with a rapidity as great, if not greater, than that of phenolsulphonphthalein; the average rate of excretion for the group being 70 per cent in one hour. Since these compounds are all quite different chemically, but have one characteristic in common (the oxygen linking the two phenol groups), and since they all show great "renal affinity," it is reasonable to assume that we have here a definite relationship between chemical structure and physiological action. As germicidal agents, all the xanthenes are inert excepting rhodamin, which comes very close to filling all the requirements. Rhodamin, which differs from resorcinnaphthalein (fluorescein) only in that the two hydroxyl groups are replaced by amino groups, is chemically stable and non-toxic, is very rapidly excreted, and kills the colon bacillus in one hour in a dilution of 1:2000, in water (10 times the strength of phenol); but when the compound is diluted *in urine* this property is entirely lost. An investigation of the nature of this interfering action in urine has not been completed.

**Summary.**—The property possessed by phenolsulphonphthalein, by virtue of which it is rapidly eliminated by the kidney, is by no means limited to this compound. Several other more or less closely related compounds show the same striking "renal affinity," and might also be of value in testing renal function were it not for the fact that phenolsulphonphthalein itself is so nearly ideal for the purpose.

Compounds of the xanthone class, that is, phthaleins (though not necessarily sulphonphthaleins) in which there is an oxygen atom linking the two phenol groups, show a similar remarkable "renal affinity."

The bromination of these compounds, both sulphonphthaleins and xanthenes, interferes with their excretion.

In view of the hitherto overlooked fact that numerous actively germicidal compounds lose their strength (owing to an as yet unexplained cause) when simply diluted with urine in a test-tube, the value of every drug used for the purpose of urinary antiseptics ought to be questioned until its antiseptic strength *in urine* has been experimentally demonstrated.

Since it has been possible to demonstrate a certain relationship between chemical structure and renal excretion, and to predict, with a reasonable degree of accuracy, which drugs will and which will not be rapidly excreted; since the synthesis of germicidal compounds, very closely related to the types excreted, has been accomplished; and since one of these germicidal compounds (rhodamin) was excreted and would have been successful but for the interfering action of the urine, the problem has been shown to be worthy of further investigation. It is hoped that these experiments may call attention to the inadequacy of the urinary antiseptics in general use, and stimulate interest in the possibilities offered by synthetic chemistry.

TABLE I  
THE EXCRETION AND THE ANTISEPTIC PROPERTIES OF THE  
SULPHONPHTHALEINS

Name	Antiseptic strength				Excretion per cent in one hour
	Kills in 1000	Fails in 1000	Inhibits in 1000	Per- sists in 1000	
Phenolsulphonphthalein	1:200	1:200	1:200	1:200	70
Thymolsulphonphthalein	1:200	1:200	1:200	1:200	70
Resorcinsulphonphthalein	1:200	1:200	1:200	1:200	70
Hydroxyresorcinsulphonphthalein	1:200	1:200	1:200	1:200	70
Cresolsulphonphthalein	1:200	1:200	1:200	1:200	70
Tetrachlorphenolsulphonphthalein	1:200	1:200	1:200	1:200	70
Phenolphthalein	1:200	1:200	1:200	1:200	70
Pyrocatechinsulphonphthalein	1:200	1:200	1:200	1:200	70
Tetrabromphenolsulphonphthalein	1:200	1:200	1:200	1:200	70
Guaiacolsulphonphthalein	1:200	1:200	1:200	1:200	70
Resorcinnaphthalein	1:200	1:200	1:200	1:200	70
Proguaiacolsulphonphthalein	1:200	1:200	1:200	1:200	70
Phenol	1:200	1:200	1:200	1:200	70

## LES NEPHRITES DE GUERRE

By P. AMICHI

(Revue de pathologie de guerre, No. 5. Vigot, Editeur. The full Article to appear in Journal of Urology, translated from the French by H. O. Mosenthal)

**ETIOLOGY.**—It is certain that nephritis is much more common under present conditions at the fighting front, than during times of peace. The disease occurs among soldiers after they have engaged in military operations for about six months. It is more common among the English troops than among the French. The higher protein consumption of the former may have a bearing in this connection. The Hindoo contingent and the officers of the other forces are not subject to the disease. It is found almost entirely among the men who live in the

trenches and those who are engaged in constructing them. It appears to be certain that exposure to cold is not the exciting cause, since nephritis is as prevalent in the warmer seasons as it is during the colder months. It is tempting to assume that the disease is the result of a bacterial infection, though at the present time proof of this contention is lacking. War nephritis is not a complication of any of the usual infectious diseases—diphtheria, scarlet fever, syphilis and others, but is a disease entity.

**PATHOLOGY.**—The kidneys may look normal on gross as well as on microscopical examination. Usually the kidneys are larger than normal and have a milky white or mottled appearance. In the interstitial tissue there are evidences of congestion, edema and exudation. The last is made up largely of polymorphonuclear cells, and may be said to be characteristic of war nephritis, since it has previously been found only on rare occasions. These inflammatory foci, if large enough, assume the appearance of the conventional miliary tubercle to the naked eye, and may be mistaken for it. They may invade the tubules and fill them; otherwise they are intact. The glomeruli are usually not involved, although in some of the later stages of the disease Andrewes has reported a proliferation of the epithelium of Bowman's capsule, followed by a gradual obliteration of the glomerular tuft. In the liver and heart the same characteristic inflammatory nodules, which have been described in the kidneys, are found. Bronchopneumonia is nearly always present. Particular stress is laid on the fact that there are lesions in organs other than the kidneys, especially the heart and the liver, and that there are characteristic inflammatory foci made up largely of polymorphonuclear cells.

**CLINICAL TYPES.** *Acute Nephritis with Edema.* This is the predominant type, constituting 90 per cent of the author's cases. At the onset there is a short febrile period, usually accompanied by general malaise; there may be dyspnea on exertion, even paroxysmal dyspnea; hematuria and albuminuria are often noted; edema, especially of the face, is generally the first symptom. All of these cases, for a short period at least, give evidence of an increased blood urea. The urinary signs and the characteristics of the edema are much like those we have been accustomed to deal with in acute nephritis with edema. In the urine there are polymorphonuclear cells which may have some relation to the characteristic inflammation described under pathology. The cases vary in intensity from those which are very mild, and in which the patients have only transient edema so that the disease may go unrecognized, to those which are very severe and are characterized by a persistence of the signs of nephritis, notably, albuminuria, recurrent edema, arterial hypertension, and impaired ability to excrete urea.

*Acute Azotemic Nephritis.*—This may escape observation, inasmuch as there may be no albuminuria and the blood urea is frequently not determined. No attention is paid to this type in any but the French literature. There is usually a marked fever, an albuminuria, which may or may not be accompanied by a hematuria, and—the constant and char-

acteristic feature—a high blood-urea. When the nephritic symptoms are not in evidence, as is usually the case, the author speaks of the condition as a *masked acute azotemic nephritis*. These patients are often thought to have "fever," "gastric fever," bronchitis, bronchopneumonia, etc. Headache, epileptiform seizures, delirium and asthma may divert attention to the nervous system, when in reality it is the nephritis with the resulting increase in the blood-urea which is responsible for these signs. At times jaundice is present. In this *acute azotemic nephritis with jaundice* renal lesions are found at autopsy, the blood-urea is high and the spirochæta *icterohemorrhagiae* is supposed to be the cause.

**TREATMENT.**—In the early stages no solid food is given and fluids are forced. While there is an azotemia the diet should consist exclusively of milk. When the azotemia disappears, no restrictions in the diet, except as regards salt, are necessary. In conjunction with the salt restriction, theobromine (up to 5 gm. a day, though more than 3 gm. is often poorly tolerated) may be used. After apparent recovery, the ability to excrete urea should be measured by Ambard's Coefficient, and the protein of the diet regulated accordingly.

**PROGNOSIS.**—The immediate prognosis in acute azotemic nephritis is not so good as in the edematous type. The persistence or increase of a blood-urea is of more significance in this regard than the actual height of the azotemia at the onset of the disease. However, when recovery does take place, it is more rapid than in the edematous type and it is usually complete. The acute nephritis with edema usually has a comparatively prolonged course, but the mortality is negligible. A cure within two or three weeks is the exception. Concerning the ultimate prognosis of these cases, there is no information at hand at present. It is known that some of the patients for an indefinite period may exhibit a tendency to edema, a diminished ability to excrete urea (according to Ambard's Coefficient) and occasionally arterial hypertension.

#### ON A CASE OF CHILDHOOD CONFLICTS WITH PROMINENT REFERENCE TO THE URINARY SYSTEM; WITH SOME GENERAL CONSIDERATIONS ON URINARY SYMPTOMS IN THE PSYCHONEUROSES AND PSYCHOSES

By C. MACFIE CAMPBELL, M.D.

(Abstract from the Psychoanalytic Review, 1918)

The report of a case of a seven-year-old girl who was studied at the dispensary of the Phipps Psychiatric Clinic for four years. The girl showed difficult behavior at home and at school, and made a superficial impression of being mentally defective; whereas, in reality, she was quite intelligent and very alert. She asked questions to an obsessive degree; this seemed to indicate an intense curiosity as to some special topic which did not dare to seek direct satisfaction. An unusual interest in water seemed to express the child's interest in her own urinary apparatus; her marked absorption in this topic was accompanied by certain peculiarities in relation to urination. The child was brought up in a very repressive home atmosphere, and had indulged in erotic games and ruminations; these erotic interests and activities were referred to quite

openly by the child at the end of the four years, and the rôle of these conflicts in causing the child's abnormal conduct was made clear.

The case illustrates in an unusually convincing way certain mechanisms which frequently are not realized, or at least are not so frankly admitted, by the child; there was no necessity in this case for any such subtle interpretation as that which detracts from the value of some well-known cases in the literature (cases of Freud, Jung).

The influence on the urinary mechanism of sexual factors is important not only in such disorders of the child as enuresis, but also in the psychoneuroses of the adult; this influence is at the basis of many otherwise obscure cases of dysuria and retention.

The situation is illustrated by brief references to a few cases in which the patient was treated for supposed tuberculosis of the spine, cystitis, etc., while the real trouble lay in the underlying difficulty of assimilation of the instinctive life.

## NOTES ON NEW BOOKS.

*Ourselves—A Personal and Family History Register for Preserving Records of a Private and Personal Nature, for One Married Couple and Their Children.* By JOHN MADISON TAYLOR, A. B., M. D. (Philadelphia: F. A. Davis Company, 1917.)

Years ago Francis Galton prepared an outline for family histories suitable for studies of heredity. It has long been out of print, and Dr. Taylor now provides a family book with directions for examination and blanks which no doubt will serve the purpose of recording a great deal of valuable information which cannot be trusted to memory. The book contains registers for the ancestors of father and ancestors of mother (to the 7th generation) and accompanying diagrams; pages for the personal histories of health of individuals over one year of age and blanks for phenomena of an attack of illness, injury, or operation; blanks for baby records—brief memoranda of circumstances of birth, growth, development, etc., physical and mental, up to one year; tables of standard weights and heights and circumference of head and chest; charts for recording weight and height; blanks for observations and findings of specialists in eye, ear, throat, and nose; blanks for clinical laboratory findings, urine, feces, blood, etc.; anatomical diagrams, to record site, size and character of lesions, deformities, etc.; diagrams for findings of dental surgeons—development, condition, repairs made, etc., of teeth; pages for special happenings—worthy incidents, education, tastes, distinctions, etc., all facts bearing on the evolution of personality and character; pages for photographs, at different ages, with dates; pages for handwriting, at different ages, with dates. In the appendix there are 11 chapters treating of the development of body, mind, character, and personality: The child as a problem for parents and others. The building of a citizen. How far can improved conditions of life overcome inherited tendencies? Personal hygiene. Hints and warnings in the bringing up of children, etc. A. M.

*The Elements of the Science of Nutrition.* By GRAHAM LUSK, PH. D., SC. D., F. R. S. (Edin.). Third Edition, Reset. Cloth \$4.50. (Philadelphia and London: W. B. Saunders Company, 1917.)

The third edition of this well-known book needs no introduction to the workers interested in nutrition, whether they be physiologists, chemists or physicians. Ever since the appearance of the first edition of this work in 1916, it has justly been looked upon as the authority in its field. It has served to link together the pure science of the psychological and pathological chemist and the science of the pathologist with that of the clinician. This has been an enormous task and one which has never been so successfully performed. Professor Lusk has, in the previous editions, exhibited rare judgment and critical skill in culling the most useful and trustworthy theories and experimental results from the ever-accumulating mass of literature. The present edition is considerably larger than its predecessor, and its value has developed in direct proportion to its size. The presentation is in the same

clear, simple and forceful style as previously. Professor Lusk has accomplished much for medical science by his own efforts in research and by his generous encouragement and supervision of the men associated with him. The book under consideration may be looked on as an epitome of the author's unbiased impressions, and is to be valued correspondingly. The only regret which the reader experiences in reviewing this volume is to note that "the writer desires to state that he has no intention of again revising this book." It is to be hoped that in the combined interests of physiology, chemistry and clinical medicine, Professor Lusk may reconsider his decision.

*A Dietary Computer.* By AMY ELIZABETH POPE. Cloth \$1.25. (New York and London: G. P. Putnam's Sons, The Knickerbocker Press, 1917.)

This book presents a series of tables of the composition and caloric value of foods, of carbohydrate equivalents and of recipes in a very acceptable form. The tabulations, as stated in the preface, are practical and easy to use.

*Life of Dr. Lyman Spalding.* By DR. JAMES ALFRED SPALDING. (Boston: W. M. Leonard, 1916.)

This book possesses much interest to all who are fond of medical biographies. It portrays very fully the life history of Dr. Lyman Spalding, a contemporary of Nathan Smith, Benjamin Waterhouse, George C. Shattuck, Caspar Wistar, Philip Syng Physic, John C. Warren, and other well-known medical men. Spalding obtained his medical education in the office of a preceptor, and had two brief courses of lectures at Harvard, where he received his degree. He practised medicine in a country town in New Hampshire at first, and taught chemistry for several weeks each year in the newly established medical school at Dartmouth College. He subsequently removed to Portsmouth, where he became interested in the extension of vaccination as a remedy for smallpox, and was a physician for a number of years. He was also a deft and able surgeon, and even operated for cataract. He prepared for many years "Bills of Mortality," giving the causes of death in the region of Portsmouth, and held the post of contract army surgeon to the troops in the vicinity.

He became later a lecturer in the newly established Fairfield Medical School in Eastern New York, and subsequently president of the same for several years. He taught anatomy, surgery and general medicine, and seems to have been an active-minded teacher with a genius for teaching. He spent a winter in Philadelphia, and there showed himself a deft anatomist. He made many anatomical preparations which were highly thought of. He removed subsequently to New York City, and while there originated and carried to successful completion a scheme for the preparation and publication of a National Pharmacopœia, and through his energy and persistence was able to devise a method of publication which has existed for the past century. He died in 1821 as the result of an accident.



The book has been prepared by Dr. James Alfred Spalding, his grandson, and is interesting throughout. A few letters written by Dr. Spalding and many letters written to him indicate the scope of his researches, and the interest felt in his work by eminent men in America and Europe. The preparation of the biography has involved great labor on the part of the author. The story, as he tells it, is of great interest and importance to all physicians and medical students.

H.

*Recollections of a New York Surgeon.* By ARPAD G. GERS-TER, M.D. (New York: Paul B. Hoeber, 1917.)

This handsomely-printed volume of nearly 350 pages gives an interesting autobiographical sketch of a well-known New York surgeon, born in Hungary in 1848, educated in Vienna, and transferred to New York in 1874, where he has since lived. The author relates his early experience in Brooklyn, his larger activities after he removed to New York City, his struggles and his successes. He held important positions in connection with various hospitals, notably the German, Mt. Sinai and Polyclinic Hospitals of New York, and has done excellent work as a teacher of surgery. His reminiscences of his early life in Hungary, of his student days in Vienna, and of his early experiences as a physician in general

practice in America are interestingly told. He lets us also into the inner recesses of his occupations, amusements and recreations of his later years, and gives a charming view of his manner of growing old gracefully. He has been interested in sketching, literature, music and etching, out-of-door sports, travel and camping. The volume is a distinct contribution to intimate medical biography, and is full of interest and instruction to all physicians.

H. M. H.

*The Respiratory Exchange of Animals and Man.* By AUGUST KROGH, PH. D. Boards \$1.80. (London: Longmans, Green & Co., 1916.)

Dr. Krogh has given in this book an excellent outline of the subject of respiratory exchange, stating the fundamental problems and reviewing the work done. The criticism of the literature, methods, results and conclusions are very pertinent and clearly written by a master of the subject. It is to be regretted that the book could not have been made larger, so that the various subjects could have been treated more at length, for in places there is little more than an encyclopedic recital of author and facts. The book is to be recommended to anyone who is working on or interested in gaseous exchange.

H. L. H.

## BOOKS RECEIVED

*A Clinical Treatise on Diseases of the Heart.* For the General Practitioner. By Edward E. Cornwall, Ph.B., M.D. 1917. 8°. 127 pages. Rezman Company, 1917.

*Diseases of the Skin; Their Pathology and Treatment.* By Milton B. Hartzell, A.M., M.D., LL.D. 51 colored plates and 242 cuts in text. 1917. 8°. 753 pages. J. B. Lippincott Company, Philadelphia and London.

*Birth Fractures and Epiphyseal Dislocations.* By Edward D. Truesdell, M.D. 1917. 4°. 135 pages. Paul B. Hoeber, New York.

*The Thyroid Gland in Health and Disease.* By Robert McCarri-son, M.D. (R.U.I.), D.Sc. (Belg.), F.R.C.P. (Lond.). 1917. 8°. 286 pages. William Wood & Company, New York.

*United States Public Health Service.* Annual Report of the Surgeon General for the Fiscal Year 1917. 8°. 387 pages. Government Printing Office, Washington.

*The Surgical Clinics of Chicago.* Vol. I, No. 6, December, 1917. 8°. W. B. Saunders Company, Philadelphia and London.

*The Medical Clinics of North America.* Vol. I, No. 3, November, 1917. 8°. W. B. Saunders Company, Philadelphia and London.

*Library of Congress.* Report of the Librarian of Congress, and Report of the Superintendent of the Library Building and Grounds. For the fiscal year ending June 30, 1917. 8°. 223 pages. Government Printing Office, Washington.

*War Surgery of the Nervous System.* A Digest of the Important Medical Journals and Books Published during the European War. Compiled by the Division of Brain Surgery, Section of Surgery of the Head. Office of the Surgeon General, War Department, Washington, D. C. 1917. 8°. 360 pages. Government Printing Office, Washington.

*Interstate Commerce Commission.* Thirty-first Annual Report. 1917. 8°. 213 pages. Government Printing Office, Washington.

*Science and Learning in France.* With a Survey of Opportunities for American Students in French Universities. An Appreciation by American Scholars. 1917. 8°. 454 pages. The Society for American Fellowships in French Universities.

*Manual of Medicine.* By Thomas Kirkpatrick Monro, M.A., M.D. Fourth Edition. 1917. 8°. 1045 pages. C. V. Mosby Company, St. Louis.

*District of Columbia.* Report of the Health Officer. 1917. 8°. 213 pages. Washington, D. C.

*Metropolitan Asylums Board.* Annual Report for the Year 1916. (19th year of issue.) Office of the Board, Embankment, E. C. 1917. 8°. 55 pages. Henderson & Spalding, London.

*The National Association for the Study and Prevention of Tuberculosis.* Transactions of the Thirteenth Annual Meeting, Cincinnati, Ohio, May 9-11, 1917. 8°. 588 pages. The National Association for the Study and Prevention of Tuberculosis, New York.

*Cornell University Medical Bulletin.* Volume VII, No. 2, October, 1917. Studies from the Department of Pharmacology and Materia Medica. 1917. 8°. Published by Cornell University, New York City.

*An International System of Ophthalmic Practice.* Edited by Walter L. Pyle, A.M., M.D. Medical Ophthalmology. By Arnold Knapp, M.D. With 32 illustrations. 1918. 8°. 509 pages. P. Blakiston's Son & Co., Philadelphia.

*Burdett's Hospitals and Charities.* 1917. Being the Year Book of Philanthropy and the Hospital Annual. By Sir Henry Burdett, K.C.B., K.C.V.O. Twenty-eighth Year. 1917. 8°. 1018 pages. The Scientific Press, Limited, London.

*Locomotor Ataxia (Tabes Dorsalis).* An Introduction to the Study and Treatment of Nervous Diseases, for Students and Practitioners. By J. M. A. Maloney, M.D. (Edin.) Illustrated. 1918. 8°. 299 pages. D. Appleton & Co., New York and London.

*Typhoid Fever Considered as a Problem of Scientific Medicine.* By Frederick P. Gay. 1918. 8°. 286 pages. Macmillan Company, 1918.

*Medical Society of London.* Transactions of the Medical Society of London. Volume the Fortieth. Edited by Hugh Lett, F.R.C.S., and William J. Fenton, M.D. 1917. 8°. 320 pages. Printed for the Society by Harrison & Sons, London.

- Thyroid and Thymus.* By André Crotti, M.D., F.A.C.S., LL.D. With 96 illustrations and 33 plates in colors. 1918. 4°. 567 pages. Lea & Febiger, Philadelphia and New York.
- American Gynecological Society.* Transactions of the American Gynecological Society. Volume 42. 1917. 8°. 648 pages. Wm. J. Dornan, Philadelphia.
- The Rockefeller Foundation.* Annual Report. 1916. 8°. 458 pages. The Rockefeller Foundation, New York.
- Bulletin of the Massachusetts Commission on Mental Diseases.* Edited under the Provisions of Acts of 1909, Chapter 504, Section 6. By Walter E. Fernald, M.D., Geo. M. Kline, M.D., E. E. Southard, M.D. 1917. Vol. 1, Nos. 1 and 2. 8°. 303 pages. Wright & Potter Printing Co., Boston.
- Western Reserve University, Cleveland.* Collected Papers from the H. K. Cushing Laboratory of Experimental Medicine. Edited by G. N. Stewart, M.D., Director. Volume V, 1916-1917. 8°. 325 pages. Cleveland.
- Navy Department, Bureau of Medicine and Surgery.* Annual Report of the Surgeon General, U. S. Navy, Chief of the Bureau of Medicine and Surgery to the Secretary of the Navy for the Fiscal Year 1917. 8°. 118 pages. Government Printing Office, Washington.
- Manual of Splints and Appliances for the Medical Department of the United States Army.* Report of a Board Convened for the Purpose of Standardizing Certain Medical Department Supplies. Lieut. Colonel William L. Keller, M.C., Major Robert B. Osgood, M.R.C., Major Alexander Lambert, M.R.C., Major Joseph A. Blake, M.R.C., Captain W. S. Baer, M.R.C., and Captain Nathaniel Allison, M.R.C. 1917. 32°. 208 pages. Oxford University Press, New York.
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# BULLETIN

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## CERTAIN CLINICAL ASPECTS OF PEPTIC ULCER WITH SPECIAL REFERENCE TO ROENTGEN-RAY DIAGNOSIS AS OBSERVED IN A STUDY OF 743 CASES<sup>1</sup>

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In a paper presented at the meeting of the Association of American Physicians in 1912, one of us presented a paper on a clinical study of 1000 cases of ulcer of the stomach and duodenum, and again in 1913 we presented our studies on the value of the X-ray in the diagnosis of this affection. Since then a further series of 743 cases has been studied by us; not only have these cases been followed clinically, but a careful X-ray

study was made in every instance. The method followed was identical with that published in our former paper. The cases were first gone into clinically, and then without any note being given as to the nature of the disorder were sent for X-ray examination. The two reports were then placed side by side in order to determine how closely the clinical and X-ray diagnoses corresponded.

The 743 cases may be divided into three groups.

*Group I.*—Cases in which there was an operation, and in which the diagnosis was definitely proven. There were 185 of these cases.

*Group II.*—Cases which presented such typical clinical symptoms as well as positive X-ray signs of peptic ulcer that the correctness of the diagnosis was positive. These cases numbered 323.

*Group III.*—Somewhat doubtful cases which presented many of the signs and symptoms of ulcer, but lacked some important signs. In the larger number of these cases the X-ray findings were quite definite. There were 235 of these cases.

*Group I.*—This group represents the most important in this series of ulcer cases, inasmuch as the diagnosis was definitely confirmed in all instances by operation. It is of interest to note the incidence of the clinical signs in these cases.

Of the 185 patients 132 were males and 53 females. Table II shows the number of cases observed in males and females according to age.

TABLE I.—ILLUSTRATING THE INCIDENCE OF IMPORTANT SIGNS AND SYMPTOMS IN 743 CASES OF PEPTIC ULCER.

	Cases proven by operation 185	Un-doubted cases of ulcer not confirmed by operation 323	Somewhat doubtful cases 235	Total 743
Definite history of ulceration . . . . .	163	301	158	622
Pain . . . . .	169	297	221	687
Tenderness . . . . .	160	293	188	641
Vomiting . . . . .	116	208	166	490
Hematemesis . . . . .	32	67	89	188
Melena . . . . .	89	155	101	345
Occult blood . . . . .	103	205	108	421
Normal acidity . . . . .	54	120	41	215
Hyperchlorhydria . . . . .	68	95	77	240
Hypochlorhydria . . . . .	42	62	31	135
Positive X-ray findings . . . . .	147	272	210	629

<sup>1</sup> Presented at the meeting of the Association of American Physicians, Atlantic City, May 8, 1918.



TABLE II

Years	Males	Females	Total
10 to 20 .....	26	4	30
20 to 30 .....	44	11	55
30 to 40 .....	36	32	68
40 to 50 .....	21	3	24
50 to 60 .....	5	3	8

Of the 185 cases a direct history of ulcer was present in 163 (88 per cent); pain in 169 (90 per cent); a tender epigastric area in 160 (86 per cent); vomiting in 116 (63 per cent); hematemesis in 32 (17 per cent); melena in 89 (48 per cent). The stools were examined for occult blood in 128 instances, the findings being positive in 108 (84 per cent).

Of the 185 cases the gastric secretion was examined in 164.

Normal acidity was observed in.....54 cases or in 32 per cent. Hyperchlorhydria was observed in.....63 cases or in 41 per cent. Hypochlorhydria and anacidity in....42 cases or in 26 per cent.

The percentage of cases of hyperchlorhydria in the series greatly exceeds that in our former series, which is due to the fact that many of these cases were examined by means of the Rehlfuss fractional method and thus in many which apparently had presented a normal acidity or subacidity there was in fact hyperacidity.

The X-ray findings in this series of cases are very interesting, inasmuch as the results were definitely checked up by operation.

In the 185 cases of ulcer, the diagnosis as made by the X-ray was verified in 147 (79.4 per cent). Of these 147 cases, in 68 the ulcers were duodenal (46.2 per cent), in 53 gastric (36 per cent), in 17 pyloro-duodenal (11.5 per cent); in the remaining 8 (5.2 per cent) the location of the ulcer was undetermined. In these 8 cases no constant filling defect was obtained, but the functional activity of the stomach was so characteristic that there was no doubt as to the nature of the lesion. Attention will later on be drawn to the importance of this finding, even when no persistent filling defect is revealed.

There remain 38 cases (20 per cent) in this series in which the X-ray findings were either not characteristic or pointed to other conditions.

Of these there was nothing abnormal revealed in 7 instances; in 21 the diagnosis of gall-bladder adhesions was made; in 5, of chronic appendicitis and adhesions in the cecal region, and in 5 the whole picture suggested an enteroptosis. In the 21 cases suggesting gall-bladder adhesions there were filling defects in 8, but these gave the impression of being produced by adhesions and not by ulcer; in 5 instances the diagnosis seemed uncertain, but evidences pointed rather to the gall-bladder, and in the remaining 8 instances the findings were definitely those of a gall-bladder affection.

*Group II.*—In this group are included those cases which presented such typical clinical signs as well as positive X-ray findings of ulcer that the diagnosis could hardly be questioned. There were 323 cases in this group. Table III shows the number of these cases observed in males and females, according to age.

TABLE III

Years	Males	Females	Total
10 to 20 .....	14	22	36
20 to 30 .....	21	57	78
30 to 40 .....	28	79	107
40 to 50 .....	39	10	49
50 to 60 .....	32	8	40
60 to 70 .....	13	0	13
	147	176	323

In this group of 323 cases there were 301 presenting definite ulcer histories (93 per cent); pain was present in 297 cases (91 per cent); a tender epigastric area in 293 (90 per cent); vomiting in 208 (61 per cent); hematemesis in 67 (20 per cent); melena in 155 (48 per cent). The stools were examined in 255 instances for occult blood, which was found present in 205 (81 per cent).

Of the 323 cases the gastric secretion was examined in 277 instances.

Normal acidity was observed in.....120 cases or 43 per cent. Hyperchlorhydria was observed in..... 95 cases or 33 per cent. Hypochlorhydria and anacidity in..... 62 cases or 24 per cent.

X-ray findings in this group were even more definite than in Group I. Of the 323 cases, positive X-ray findings were obtained in 272 (84 per cent).

Of these 272 cases 117 were duodenal ulcers (43 per cent); 109 gastric ulcers (40 per cent); 38 pyloro-duodenal ulcers (14 per cent) and in 8 (3 per cent) the location remained undetermined. A filling defect was absent in the 8 undetermined cases; but here too the functional activity of the stomach was so definite that a positive diagnosis of ulcer was made with almost absolute certainty.

There were 51 cases (15.6 per cent) in this group in which the X-ray findings were either uncertain or pointed to some other pathological conditions.

Of these cases no abnormality was discovered in 12 instances; in 29 the diagnosis of gall-bladder adhesions or of a chronic appendicitis was made. In the 29 cases a filling defect was observed in 11, which was regarded as due to adhesions and not to ulceration; notwithstanding these X-ray findings the clinical signs were so definite that the diagnosis of ulcer appeared justifiable.

*Group III.*—We have put in this group those cases that presented many of the manifestations of ulceration, but in which there still appeared some element of doubt as to diagnosis. In some of these cases there were few clinical signs except hemorrhage, while the X-ray pointed to ulcer; in other cases the clinical signs indicated ulceration, while the X-ray either revealed no lesion in the stomach whatever or else pointed to some affection in a more distant portion of the abdominal cavity. In no inconsiderable number of cases the history of ulceration was so definite that the diagnosis appeared unmistakable; yet the gastric secretion presented an absence of free hydrochloric acid, there was no history of hemorrhage, nor was occult blood found in the stools at repeated examinations.

The diagnosis was definitely cleared up in many of these instances by positive X-ray findings.

Table IV presents the cases of ulceration observed in this group, in males and females, arranged according to age. Of the 235 patients 121 were males and 114 females.

TABLE IV

Years	Males	Females	Total
10 to 20 .....	4	6	10
20 to 30 .....	15	8	23
30 to 40 .....	29	49	78
40 to 50 .....	37	28	65
50 to 60 .....	32	15	47
60 to 70 .....	4	8	12

In this group of 235 cases there were 158 presenting a definite ulcer history (67 per cent); pain was present in 221 cases (94 per cent); a tender epigastric area in 188 (80 per cent); vomiting in 156 cases (66 per cent); hematemesis in 89 (37 per cent); melena in 96 (40 per cent). The stools were examined in 133 instances for occult blood, which was found present in 108 (81 per cent).

Of the 235 cases the gastric secretion was examined in 149.

Normal acidity was observed in.....41 cases or 27 per cent.  
Hyperchlorhydria was observed in .....77 cases or 51 per cent.  
Hypochlorhydria or anacidity in.....31 cases or 22 per cent.

In this group of 235 cases the X-ray findings were so outspoken in 218 instances (89.7 per cent) that, notwithstanding the absence of certain of the clinical signs, the diagnosis of ulcer seemed justified. Of the 210 cases in 80 (38 per cent) there were duodenal ulcers; in 88 (42 per cent) gastric ulcers; in 25 (11 per cent) pyloro-duodenal ulcers, and in 17 (8 per cent) the location of the lesion remained undetermined. In these 17 cases a filling defect was not observed, yet here too the functional activity of the stomach was so characteristic that there remained but little doubt as to the diagnosis. There remain 25 cases in this series (12 per cent) in which the X-ray findings were not characteristic of ulcer or else pointed to other conditions. Of these nothing abnormal was observed in 8 instances in the plates; in 9 gall-bladder adhesions were shown, and in 8 chronic inflammatory changes in the right lower quadrant indicating the presence of a chronic appendicitis.

The X-ray findings in uncomplicated cases of gastric and duodenal ulcer are, as a rule, very definite as well as constant. The signs ordinarily observed are not unlike those described by us in a former communication.

It is only within the last years that we are beginning to observe results upon which reliance may be placed. The old theory that it was possible to diagnose ulcer from the adherence of bismuth to the raw surfaces has now been practically abandoned, inasmuch as experience has taught us that this rarely happens because the irritability of the raw surface produces hypermotility with violent contractions, which render it almost impossible for the bismuth to adhere to the raw surfaces. At present we lay stress on the way the stomach and intestines function as well as upon the actual demonstration of the ulcer. Curiously enough, the diagnosis of duodenal ulcer is much simpler than that of gastric ulcer.

We can practically always rule out the presence of a simple duodenal ulcer, but we cannot always rule out gastric ulcer.

The main distinction lies in the fact that in an irritating lesion of the stomach, such as ulcer, the consequent hypermotility causes a tonic contraction of the pylorus with retention of the gastric contents over a shorter or longer period, as well as a deformity, according to the situation of the ulcer. On the other hand, in lesions of the duodenum, we have indeed a hypermotility not only of the duodenum, but of the stomach itself; but in this case we do not have the spastic condition of the pylorus, consequently the hypermotility produces a rapid emptying of the stomach contents. For example, in our experience, in simple ulcer of the duodenum not complicated by adhesions, we find that the stomach will invariably extrude the greater part of its contents in from fifteen or twenty minutes to an hour. There are in addition certain characteristic features connected with this lesion; we have a decided hypermotility, but the contractions are quite uniform, and there is no tendency toward hour-glass formation of the stomach. The pylorus is patulous and the bismuth flows quite freely into the duodenum. The duodenum is in very active contraction, and in many cases we find that there is a deformity in some portion of it, and this defect persists throughout the period of the examination. At times we may observe bismuth running along either side with the defect between the two bismuth currents.

In gastric ulcer we have just the reverse. There will be primary quick expulsion of contents and then the spastic condition of the pylorus appears with hour-glass formation, and we have a retention, lasting anywhere from four to six hours, according as the lesion is simple or is complicated by adhesions. In addition a filling defect is usually observed which remains constant in all examinations.

The differentiation between gastric and duodenal ulcer from clinical signs alone is often very difficult, and not a few clinicians hold that in many instances it is impossible. The X-ray findings in the two conditions, however, differ so markedly that in them we possess an almost positive means of differentiation.

In our combined series of cases positive X-ray findings were noted in 84.4 per cent of all cases examined. Of these 42 per cent represented duodenal ulcers; 39 per cent gastric ulcers; 12 per cent pyloro-duodenal ulcers; in 8 per cent the location of the lesion was undetermined.

While the functional activity of the stomach from a roentgenological point of view may indicate the presence of an ulcer, the filling defect or deformity may be absent and may not be revealed in the plates, owing to the fact that only when the lesion is situated on the anterior surface of the stomach and along the anterior surface of the lesser and greater curvatures can this condition be observed. According to our observations the functional signs are often as important as the presence of the defect in arriving at definite conclusions. This condition is especially well illustrated in the healing of ulcers (attention to which will be called later on) in which, although the defect may still remain in the form of a cicatrix, the functional activity of the stomach may have become entirely normal.

In 8 per cent of our cases there were no defects observed, yet the functional activity of the stomach pointed definitely to ulcer.

The greatest difficulties arise in the diagnosis of complicated cases; that is, when adhesions are present, due either to the healing of the ulcer or to inflammations connected with one or other of the organs in the abdominal cavity. These adhesions so frequently mask the usual findings, that it is often impossible to determine whether we are really dealing with an ulcer or whether a lesion of some other organ is causing the symptoms. Such adhesions may arise from the ulcer itself, from the gall-bladder or appendix, or there may be no adhesions at all in the region of the stomach, and the gastric findings may be due to a purely reflex condition or to spasm.

It is necessary at times, in a certain proportion of cases in which adhesions of the stomach are present, to lay especial stress upon the clinical history of the case before a final decision can be made. If the clinical signs coincide with a definite history of ulcer, we must conclude that the adhesions have taken their origin from the ulcer; if of cholelithiasis, from the gall-bladder; and so on, inasmuch as from a roentgenological point of view the appearances are frequently identical.

In 9 per cent of the cases in our series the diagnosis was rendered doubtful by the presence of adhesions.

As has been pointed out, unless due care be exercised, one may easily be misled by certain reflex or spastic conditions of the stomach. It is not uncommon to observe a stomach presenting a persistent filling defect in a definite area and continuing over a period of an hour or two—in a single instance under our observation it persisted for 48 hours. In doubtful cases, spasm of the stomach can easily be eliminated by the administration of full doses of atropin for one or two days, until the patient is well under its influence. A second examination, made under these conditions, will immediately show that the suspicious area has completely vanished, and that the condition previously observed was due to spasm.

Additional evidence of the presence of an ulcer when situated at or near the pylorus is the presence of obstructive signs produced by the cicatrix while the ulcer is healing.

Clinically, the diagnosis of *gastrectasia due to stenosis of the pylorus* is usually not difficult, especially when the cardinal symptoms of this disease are present. The vomiting of the collective type, together with peristaltic or antiperistaltic waves, suggest the diagnosis; and this becomes even more certain when remnants of food are obtained from the fasting stomach in the morning, and especially when the gastric contents are of the three-layered variety, and contain numerous sarcine; or when the rice test of Hausmann or the chlorophyll test of Boas is positive. But we all know that these findings are present only when the obstruction is marked or nearly complete, and that there is a large number of cases in which obstruction is suspected, and yet many weeks often elapse before the stenosis becomes sufficiently marked to warrant a positive diagnosis, for the symptoms already noted occur only as late manifestations of the disease, and are not present or are observed only occasionally as early signs. At times spastic

contractions of the pylorus due to former ulcers or the irritation exerted by the gastric contents upon erosions and fissures in this region afford similar signs.

In this condition, when the X-ray examination is made, a typical sack-like formation is observed, and all the bismuth rests at the bottom of the fundus. Under such conditions the examination will show a retention of contents for from 10 to 20 hours.

In the early stages of gastrectasia, that is, when the obstruction is still incomplete, the diagnosis is often very difficult. The condition is due to a partial stenosis of the pylorus, and inasmuch as the symptoms produced by it are quite vague, the condition is often overlooked, or an incorrect diagnosis is made.

The physical signs of the disease are not marked, peristalsis being usually absent and vomiting occurring irregularly, the vomitus being devoid of the usual features occurring in gastric stasis. A symptom very frequently present is pain, appearing some time after meals and becoming most intense 2 or 3 hours after the ingestion of food.

This pain is due to the pyloric spasm produced by the incomplete obstruction, and is temporarily relieved by the ingestion of food or of alkalies. As is well known, this symptom is characteristic of ulcerative lesions in the pyloric or juxta-pyloric region, but since in many instances partial obstructions have their origin in pyloric and juxta-pyloric ulcerations, this symptom is valuable as an early sign of the disease. As additional evidence of the presence of partial stenosis is the existence of gastric secretion in the fasting stomach, especially if it is observed in frequent examinations. If the fasting stomach is constantly empty of gastric secretion, partial stenosis may usually be excluded. The diagnosis may be based, therefore, on the presence of secretion in the fasting stomach, occurring continuously or intermittently, together with stasis, even of a small amount, appearing at more or less frequent intervals.

These signs appear, however, so intermittently that they are often overlooked, especially when overshadowed by the usual symptoms of dyspepsia occurring in this affection. The X-ray has given us a means of more thoroughly solving this difficult problem.

In the early stages of this condition we have active contractions with the slow extrusion of the stomach contents. Now a normal stomach extrusion gets rid of its bismuth meal in from three to six hours. Generally, we observe that the high stomach occupying the horizontal position empties itself much more quickly than the prolapsed fish-hook variety, so that it might be stated that from 3 to 4 hours is the normal rate of emptying for the horizontal stomach, and from 5 to 6 hours for the prolapsed fish-hook variety. When in these various types we note that, while the contractions are good but the expulsion of contents is slower than under normal conditions, we must consider the possibility of some beginning obstruction.

A second very significant sign is the fact that in the study of the plates we frequently observe that a portion of the stomach just within the pylorus on the greater curvature in the prepy-



loric region shows a tendency to bulge. This condition is produced by the active contraction of the stomach, forcing all of the food towards the pyloric region. The pylorus not being patent, the prepyloric portion of the stomach becomes dilated under this constant pressure, so that the plate presents the pylorus not at the end of the stomach, as it were, but with the prepyloric region extending further to the right than the pylorus, the pylorus resting on the top of the stomach, and pointing to the splenic region. The prepyloric bulging is dependent largely upon the duration of the affection. In early cases it is very slight, but as the condition advances the prepyloric bulging may reach the size of a hen's egg. If the condition persists, dilation begins to take place, and after a time practically the entire fundus yields, so that a typical sack-like formation is produced, and all the bismuth rests at the bottom of the fundus.

In 20 per cent of our cases there were evidences of obstruction with dilatation of the stomach, in 12 per cent of these partial obstruction was observed.

In a certain number of cases there are definite clinical evidences of ulceration, and yet the X-ray presents no indication whatsoever of this condition. This may be due, as we have already pointed out, in some instances, to adhesions masking the true condition, but the absence of definite X-ray signs cannot always be traced to this factor. It happens at times that a complicating chronic appendicitis or cholecystitis may be so marked as to mask any findings in the stomach itself, and the significance of a small filling defect might easily be overlooked.

In one of our cases (Dr. B.), a man of 64 years of age, who had presented definite clinical signs of duodenal ulceration for years, and in whom the X-ray findings had been positive 4 years previously, our examination gave evidence of gall-bladder adhesions and no signs of ulceration. At operation a large duodenal ulcer with adhesions was found. In another instance (Mrs. B.), the X-ray findings pointed to a chronic appendicitis, whereas the clinical evidences were definitely in favor of ulcer. At operation a definite indurated duodenal ulcer was found.

In our entire series there were 3 per cent of cases of ulceration in which the X-ray signs gave no evidences of the actual condition, and in 15 per cent they were indefinite.

Although ulcerations are not always revealed by X-ray examinations, there are many cases of ulcer doubtful from a clinical standpoint in which the ray will clear up the diagnosis. In two of our cases the clinical signs were indefinite, but suggested an appendicitis; the X-ray was definite as to ulcer in both instances. Appendectomy was performed, and only temporary relief was afforded; there was subsequent gastric hemorrhage and finally operation revealed an ulcer in each instance. Another patient (Mr. McE.), a man aged 66, gave a history of very indefinite gastro-intestinal symptoms. The X-ray revealed ulceration; a sudden large gastric hemorrhage showed the correctness of this finding. The X-ray is, therefore, of the greatest help in pointing to the current diagnosis in doubtful cases. In 1 per cent of such indefinite cases in our entire series the X-ray cleared up the diagnosis.

There are cases, however, in our experience in which the diagnosis of either chronic appendicitis or cholelithiasis is made not only from a clinical, but also from a roentgenological standpoint, but which at operation present no evidence of such conditions, ulceration of the stomach or duodenum being found, although the X-ray plates have shown no evidences pointing to either affection. Finally, there still remains another group of cases in which the ulcerations are of the so-called mucous type. These are easily demonstrated by means of the X-ray, but are rarely observed at operation unless the stomach itself be incised. It frequently happens that such cases come to operation, and yet no abnormality is observed at the exploration. This is due to the fact that while both mucous and penetrating ulcers are alike easily discernible by means of the X-ray, we have as yet no means of distinguishing between such conditions, except in those instances in which large indurated or perforating ulcers are present.

In the X-ray study of *gastric ulcer* the differential diagnosis between this condition and *gastric carcinoma* is often very difficult. It is still a much debated question whether carcinoma of the stomach has its origin primarily as such, or is the result of a transition from an ulcer. If the latter view be correct, one can readily understand the difficulty in determining when the benign condition enters the stage of transition into malignancy. The situation of both ulcer and carcinoma is very frequently the same, although we observe ulcer more frequently than carcinoma on the lesser curvature.

In the differential diagnosis between the two conditions the points to be taken into consideration are as follows:

1. *Peristalsis*.—In ulcer there is always hypermotility with a spasm of the pylorus and more or less retention of contents. In carcinoma, unless there is obstruction, there is always hypermotility with rapid evacuation of contents.

2. *Position*.—Ulcer is generally observed on the lesser curvature near the pylorus, although it may occur on the greater curvature and is frequently found in the duodenum. Carcinoma may occur in any part of the stomach. The invasive lesions are more frequently seen on the lesser curvature near the pylorus, and less frequently on the greater curvature. The massive growths are more generally seen on the greater curvature.

*Filling Defect*.—In ulcer the filling defect is much smaller and is not apt to have the immediate peristaltic waves interfered with, although, if the inflammatory area be large, there may be a dead area surrounding the filling defect. In carcinoma the filling defect is generally surrounded by an invasive area, which, although not appearing on the plate, interferes with motility, producing an apparently large dead area. In ulcer of the pylorus there is a filling defect, but it does not generally assume a crater-like appearance. Carcinoma of the pylorus in the earliest stage is generally annular and produces a crater-like appearance.

When any of these conditions pass on to the obstructive stage, the change that is caused by the dilatation may mask the signs associated with the filling defect.

In our experience, in the very early stages of gastric cancer, it is frequently impossible to determine whether we are dealing with a malignant or a simple ulceration. Our main aim, however, is to decide whether the lesion at hand is really an ulcer or not. Inasmuch as indurated gastric ulcers have at times a tendency to become malignant and produce roentgenograms similar to those which are cancerous, they must be included in the same class. The exact diagnosis must be cleared up by further investigation into the clinical history and by the examination.

But even under these conditions there are many cases in which the diagnosis may still remain in doubt until operation, and, in some, microscopic examination of the specimen after removal may be necessary in order to establish the true nature of the disease.

In our series there were 1.1 per cent of cases in which the ulcer was mistaken for carcinoma; in a larger percentage, however, carcinoma was mistaken for ulcer.

Now that we have taken up the positive phase of the diagnosis of ulcer, it is wise to draw some conclusions as to the *negative findings*. In the first place we believe that we can rule out positively the presence of a duodenal ulcer. If we observe that the stomach contents are not expelled promptly, and that the greater portion remains after the lapse of an hour, we can maintain confidently that the trouble is not in the duodenum. Even in the old chronic ulcer, with adhesions, the motility is so marked that it cannot be overlooked. The negative diagnosis of gastric ulcer is also of importance. However, so many complicating phases are present in these cases that the retention of bismuth in the stomach does not appear to have quite the same significance as the hypermotility in duodenal ulcer. The absence of a filling defect in the stomach or of a deformity of the duodenal cap is a significant sign pointing against ulcer.

As has been shown, in gastric ulcer, we have a spastic retention. In simple atony and in prolapse we may have retention and yet the spastic character of the retention is not present, nor is there any tendency toward the formation of an hour-glass stomach.

The absence of any of the positive signs of ulcer by means of the X-ray examination has been of the greatest help to us in excluding the presence of ulcer. This method has been especially helpful in the diagnosis of atypical conditions and affords us the most positive method of excluding ulcer.

There have been 698 cases in which we have been able to exclude the presence of ulcer by this method of examination.

Another very important point which our X-ray studies have brought out in connection with ulcer is that the degree of healing can be determined by this method. We were among the first to call attention to the fact, and other clinicians have since corroborated this finding. In ulcer, when the patient is given a rest-cure treatment, all symptoms gradually disappear and the patient becomes, comparatively speaking, well. This usually takes place in from 4 to 5 weeks. At the end of this time, however, if a second bismuth examination is made, we often find the same characteristic signs as in the first ulcer,

though the patient shows no symptoms whatever. In a series of ulcer cases, that have been examined in from 3 to 4 weeks after an absence of symptoms, we have frequently found but little change in the defect or motility of the stomach.

When these patients are given the ordinary diet these symptoms may recur in a short time. If treatment is continued, however, our experience has demonstrated that, as the ulcer continues to heal, the motility of the stomach returns to a more normal condition, and by making repeated X-ray observations over a long period of time we can observe when the ulcer has healed.

There can be no question that this is one of the most important findings of this work, inasmuch as, until this method was employed, there was absolutely no means of determining whether an ulcer had healed or not. Our only means of determining this question has been a return of symptoms when the patient was placed upon an ordinary diet, and this simply meant a relapse for the patient. By means of the X-ray examination made from time to time we are enabled to determine the progress of healing. This method has been utilized to great advantage by us in 321 of our cases (43 per cent).

There is another fact of great importance connected with the healing of ulcers brought out by this method of examination. We observed that not infrequently, after an ulcer has completely healed, another ulcer may take its origin, sooner or later, either at the same location or at another, either in the stomach or duodenum. This finding was demonstrated by us in 64 instances (8 per cent). In the largest number of these cases there can be but little question but that the ulcer must have been caused by some focal infection for, curiously, in some instances after the removal of the infection there was no further recurrence.

Finally, important evidence is further obtained by means of the X-ray as to the extent of the ulcer and degree of induration, as well as the degree of obstruction, and thus we are guided in determining in a measure whether surgical interference should or should not be undertaken. Of the 185 of our cases which were operated on, the X-ray demonstrated the necessity of the operation in 147 cases (79.4 per cent).

*Conclusions.*—From our studies on the many cases of peptic ulcer in which X-ray examinations were made, we believe that we are justified in drawing the following conclusions:

1. The X-ray offers most valuable assistance to the diagnosis of peptic ulcer, and although this method is not yet sufficiently well developed to be relied upon alone without entering into the clinical aspects of the disease, it is of the greatest diagnostic help in obscure cases.

Positive X-ray findings are noted in about 84 per cent of cases of peptic ulcers and in 79 per cent of cases operated upon.

2. In duodenal ulcer there is excessive hypermotility of the stomach with rapid evacuation of the contents, so that the greater portion is extruded within the first half hour; there is hypermotility of the duodenum with formation, usually, of a deformity which remains fixed in all of the examinations.

3. The diagnosis of gastric ulcer is dependent upon two conditions, namely, the functioning of the stomach, and the

finding of the filling defect. It is only when the filling defect is situated along the anterior surface of the stomach and along the anterior surface of the lesser and greater curvatures that it can be demonstrated. On the other hand, it matters not what the situation of the ulcer is, the functions of the stomach are materially affected. We have in this condition an excessive irritation from the ulcer, with consequent hypermotility and a spastic condition of the pylorus, so that for the time being there is practically no expulsion of bismuth. It is only when the spasticity relaxes that a portion of the bismuth is expelled. In gastric ulcer, wherever its situation, we can always look for a certain amount of retention of contents. There is always a more or less marked hour-glass formation. According to our observations the functional signs are often as important as the presence of the filling defect in arriving at definite conclusions, inasmuch as in 8 per cent of our cases, although there were no defects found, the functional changes pointed definitely to ulcer.

4. The greatest difficulties arise in the diagnosis of complicated cases; that is, when adhesions are present. These so frequently mask the usual findings that it is often impossible to determine whether there is really an ulcer of the stomach at hand or a lesion of some other organ. When the ulcer is situated at or near the pylorus, signs of partial obstruction frequently aid in establishing the diagnosis.

5. The X-ray affords an almost absolute means of differentiating between gastric and duodenal ulcer.

6. By means of the X-ray examination we can generally rule out the presence of ulcer.

7. We can approximately determine the degree of healing as well as recurrence of an ulcer which cannot be as certainly determined in any other way.

8. One can obtain sufficient evidence as to the extent and induration of the ulcer and degree of obstruction to guide us, in a measure, as to the necessity of surgical intervention.

## EXPERIMENTAL MENINGOCOCCUS MENINGITIS

By CHARLES R. AUSTRIAN, M. D.

(From the Medical Clinic, The Johns Hopkins Hospital)

In 1915 Black<sup>1</sup> published observations concerning the use of prophylactic vaccine to prevent the development of epidemic cerebrospinal meningitis. Shortly thereafter this study was undertaken experimentally to test the efficacy of the procedure.

Owing to the proximity of the laboratory to the wards of the hospital, and because of limited funds, monkeys were not to be had for the experiments, and the attempt to utilize a smaller animal was made. The rabbit was chosen, and a satisfactory technique for the production of meningeal infection was elaborated, the details of which have been published in a previous communication.<sup>2</sup> In brief, it was found that a needle can be readily introduced into the spinal canal of a rabbit, that material can be injected through it into the lumbar (or other region) of the canal, and that substances thus injected are rapidly spread throughout the subdural space. Spinal puncture was always carried out only after the animal had received a light ether narcosis.

The disadvantages inherent in the use of rabbits in the study of meningeal disease are two: First, it is difficult to avoid injury to the spinal cord when injections are made; secondly, the spinal fluid, normally and in disease, is so scanty that withdrawal of it by aspiration is impossible and one is thus deprived of the means of *intra-vitam* determination of the presence or progress of infection.

The method perfected, suspensions of meningococci were introduced into the spinal canal of rabbits of approximately the same size and weight and that were kept under identical conditions. It was found that white rabbits were more desirable than other varieties.

Some of the strains of meningococci were obtained from the Rockefeller Institute through the courtesy of Dr. Louise Pearce; others were isolated from the spinal fluid of patients with epidemic cerebrospinal meningitis. The variable virulence of the organisms necessitated the use of a number of strains before a suitable one was obtained. The particular one used in most of the following experiments was a relatively attenuated one recovered from a case of subacute meningitis (Thomson) admitted to the medical service of The Johns Hopkins Hospital.

This strain, like others employed, was identified as a pure meningococcus by morphological and staining characteristics, cultural and fermentation tests, and by agglutination with anti-meningococcus serum. The cocci were planted on blood- or serum-agar slants and incubated for 20 hours at 37° C. A homogeneous suspension of the growth on the surface of two such slants was made in sterile 0.85 per cent salt solution and 0.5 to 1.5 c. c. were used for the injections. All suspensions were injected within 45 minutes of preparation.

Some of the animals that received injections died within 12 to 24 hours, and at autopsy showed no gross lesion except hyperæmia of the meningeal vessels. The larger number developed a typical clinical picture of meningitis and showed characteristic anatomical changes. The following two protocols are illustrative:

January 12, 1915. Rabbit 317. White, female, weight 2000 grams. The lower back was clipped, shaved and cleaned with tincture of iodine. The animal was then etherized and a needle was introduced between the two upper lumbar vertebrae. Recovery from narcosis was complete in 10 minutes and 1.5 c. c. of a suspension of meningococci prepared as described were slowly injected. Following a period of restlessness, paresis of the hind quarters and helpless inertia of 30 minutes' duration, the animal

<sup>1</sup> Black, J. L.: Jour. A. M. A., 1914, LXVIII, 2126.

<sup>2</sup> Austrian, C. R.: BULL. JOHNS HOPKINS HOSPITAL, 1916, XXVII, 237.



recovered except for weakness of the left hind leg. Sixteen hours later, the rabbit was found lying on its right side with spastic hind quarters, extended forelegs, clonic jerking of the head and irregular respiration. Two hours later, there were retraction of the head, rigidity of the cervical muscles and clonic convulsions. Twenty-four hours after injection the animal was found dead.

*Autopsy.*—Well-nourished rabbit in position of opisthotonus. Except for the lesions in the nervous system the viscera appeared normal. The spinal meninges were moderately injected, a small amount of turbid fluid had accumulated over the thoracic cord, and over the dorsum of the medulla, pons and cerebellum there was a very turbid, gelatinous exudate. Over the convexity of the brain there was an unusual grade of congestion of the dura and pia, and the same condition was noted over the base of the brain with a small amount of gelatinous exudate. There was no marked reaction along the olfactory bulbs. Fresh smear preparations from the dorsum of the pons showed very many polymorphonuclear leucocytes and a few red corpuscles. Stained smears showed clumps of pus cells and myriads of gram-negative diplococci, a number of them intracellular. Cultures from the exudate showed typical meningococci. Smear preparations and cultures from the nose failed to show the organism.

January 12, 1915. Rabbit 318. White, female, weight 2100 grams. This animal was prepared in the same way as Rabbit 317 and received an intraspinal injection of 1 c. c. of the same suspension of organisms. The injection was followed by coma of 25 minutes' duration, after which the animal was ataxic for a short time. Four hours after injection the animal was dull, its head was strongly retracted, respiration irregular, and there were jerkings of the hind legs. Seventeen hours after injection the rabbit was found dead in its cage.

*Autopsy.*—Well-nourished rabbit with head sharply retracted. Large blood clots in the nose. Except for the lesions in the nervous system the viscera appeared normal. The striking finding in the central nervous system was the extreme congestion of the meninges. The hyperæmia extended into the sulci of the brain and was more marked over the base than over the convexity. There was a small excess of cloudy fluid over the dorsal aspect of the brain-stem and many minute hæmorrhages beneath the pia. The olfactory bulbs showed nothing striking, but the nasal mucosa was very much injected and showed a number of small hæmorrhages. Smear preparations from the exudate at the base of the brain and over the pons showed numerous polymorphonuclear leucocytes and gram-negative diplococci, mainly extracellular and in various stages of degeneration. Meningococci did not grow in cultures from nose or spinal exudate.

In six of the ten animals included in this series, the meningitis that developed ran a rapidly lethal course in from 20 to 36 hours. In three, after a period of symptoms varying from one to five hours, recovery followed. It was not possible to produce a chronic form of the disease in untreated animals.

It is worthy of note that smears and cultures from the nasal mucous membrane of Rabbit 317 showed the presence of meningococci, for this observation definitely establishes the finding of Flexner that this organism may be excreted through the nose.

The reaction to infection in the rabbit differs from that seen in man and in monkeys in the small amount of fibrin in the exudate and the scanty increase of cerebrospinal fluid. In only two of the ten animals included in this group did a blood invasion occur. It was apparent that cocci introduced into the spinal canal in the lumbosacral region soon became distributed along the meninges and gave rise to an inflammatory reaction most marked at the base of the brain. This finding corre-

sponds to that of Flexner in the experimental meningitis of monkeys, and, as he has indicated, is evidence that speaks against a basal localization as indicative of infection from the nose.

At this juncture we departed from our original purpose and attempted to find out whether or not a meningococcal meningitis could be produced by routes of infection other than the intraspinal one.

The idea generally accepted since the time of Weigert of the direct invasion of the meninges by the passage of meningococci from the nasal mucosa through the ethmoid sinus to the base of the brain seemed to us, as it had to others, open to question. The occasionally demonstrated occurrence of a bacteræmia in the course of the disease in man might indicate as well the septic nature of the disease with a metastatic localization in the meninges as an overflow into the blood stream from a primary meningeal focus. The latter view seems more probable when it is recalled that the blood culture is more likely to yield positive findings early in the course of the illness. Moreover, it seems illogical that the direct route should be the path of election, as the mucous membrane of the nose and the meninges themselves, unless already diseased, should act, in a measure at least, as a protective barrier.

With these ideas in mind, the following experiments were made:

*Series A.*—Each of 20 rabbits was given an injection of varying amounts of the standard suspension of meningococci (Thomson) into the nasal mucous membrane. At different intervals after treatment the animals were killed by a blow on the head and cultures and smears of the heart's blood and meninges were studied.

Not one of these animals developed meningitis. In not one could the organism be demonstrated in smear or culture from the cerebral or spinal meninges. Two of the rabbits developed positive blood cultures, but the blood invasion may have been due to a direct injection into a small blood vessel of the nose.

Similar results were obtained when a fresh ointment of meningococci in vaseline was roughly rubbed into the mucous membrane of the nose.

*Series B.*—Each of a group of 15 rabbits was given an injection of the standard suspension into an ear vein, and at intervals varying from 10 to 50 minutes after inoculations cultures were made of the blood and from the meningeal surfaces.

The micrococci disappeared from the peripheral circulation of these animals in from 15 to 75 minutes. None of this group developed meningitis and none showed the organisms in smears or cultures from the meninges.

The inability to infect the normal cerebrospinal canal of rabbits either by the intranasal or the intravenous injection of the meningococcus was definite.

Mindful of the recognized fact that the interchange between the meningeal and systemic circulations is enhanced by hyperæmia of the choroid plexus and of the meningeal vessels, the effect of preliminary irritation of the meninges and subsequent

possible infection through the nasal cavity or through the general circulation was studied.

Rabbits that received a subdural injection of fresh or of inactivated rabbit serum did not develop any symptoms except those due to temporarily increased intracranial pressure (dyspnea, twitching or coma of short duration), symptoms identical with those following the introduction of an equal quantity of salt solution. When killed and examined within 30 to 60 minutes after injection, marked engorgement of the meningeal vessels was found.

*Series C.*—Fifteen normal rabbits were each given an intraspinal injection of 0.5 c. c. of normal rabbit serum. Thirty to sixty minutes after this preliminary treatment each received 1 c. c. of the standard suspension of meningococci by direct injection or by rough inoculation into the mucous membrane of the nose. In none were the organisms demonstrable in smears or in cultures made from the surface of the meninges, 5, 10, 15 or 24 hours after the organisms had been introduced.

*Series D.*—Each of 20 rabbits received a preliminary intraspinal injection of 0.5 to 1.0 c. c. of normal rabbit serum and 30 to 50 minutes later was given an injection of the standard suspension of meningococci into an ear vein. The exact technique of this procedure and the results of this experiment are shown in the appended protocol:

March 12, 1915. Rabbit 345. White, male, weight 1800 grams. The lower back was clipped and cleaned with tincture of iodine and the animal was given a light ether anæsthesia. A needle was inserted into the spinal canal in the lumbar region and 2.0 c. c. of normal rabbit serum were injected. Injury of the cord caused twitching of the tail and spastic palsy of the left hind leg, and dyspnea, coma and ataxia developed. Thirty minutes later 2.0 c. c. of the standard suspension of meningococci were injected into the ear vein. Three hours after the intravenous injection the animal was dull, inert, but markedly hyperæsthetic to sound and touch. Twenty hours after injection the animal was very excitable when aroused, inert when undisturbed. There was no muscle rigidity, no retraction of the head. Eight hours after this observation the animal was killed.

*Autopsy.*—Well-nourished rabbit. General examination was quite negative. The meninges over the spinal cord showed nothing strikingly abnormal. There was a punctate hæmorrhage where the needle had penetrated the cord. Over the dorsal surface of the pons there was a marked excess of turbid fluid containing fine flecks of fibrin. The vessels of the pia and dura were markedly congested, and over the base of the brain there was a definite excess of sero-fibrinous exudate. Stained smears from the exudate showed polymorphonuclear leucocytes and many gram-negative diplococci, mainly extracellular. Cultures from the surface of the pons and the base of the brain gave a pure culture of typical meningococci. Cultures from the heart's blood and spinal meninges were sterile.

In 20 experiments of this type, eight of the animals died within 8 to 12 hours after injection without clinical evidence of meningeal irritation and at autopsy no meningitis was found. From the meninges of two animals killed one hour after intravenous injection, the meningococcus was identified in smears, and from the spinal canal of one of them the organism was obtained in culture. Three others of this series developed a typical fatal meningitis. The remaining seven

animals after symptoms lasting 30 minutes to two hours recovered completely. It is unfortunate that some of these were not sacrificed at short intervals to determine if the cocci had penetrated the central nervous system.

This experiment demonstrated that meningococcal sepsis in the rabbit may lead to the development of a metastatic meningitis when there is a pre-existent hyperæmia of the meninges. The development of an outspoken inflammation of the cerebral and spinal membranes was inconstant, but the clinical and anatomical findings were characteristic.

The results of the foregoing studies seemed clearly to justify the following conclusions:

- (1) The cerebrospinal canal can be infected by way of the blood stream.
- (2) Though under normal conditions the presence of a bacteræmia does not lead to the development of meningitis, when a condition of hyperæmia of the thecal vessels exists, meningeal inflammation may result.
- (3) Neither when normal conditions are present nor when meningeal irritation has been induced do meningococci introduced into the nasal mucous membrane gain access to the meninges.
- (4) The demonstration of meningococci in the nasal secretion is to be interpreted as evidence of the excretion of these organisms by this route, but the conclusion is not necessarily warranted that they find a direct portal of entry to the meninges by the same channel.

These observations seem important from an etiological standpoint. They indicate the probability that epidemic cerebrospinal meningitis, as it occurs in man, is to be regarded as a metastatic disease developing in the course of a general infection, rather than as the evidence of a primary local disease. They do not necessarily indicate the portal of entry of the invader, nor antagonize the view that the cocci are taken into the body through the upper respiratory tract, a fact apparently established.

The observation that meningococcal sepsis in rabbits is followed by the development of meningeal disease only when the meninges are not in a normal state is suggestive and may explain in part, at least, the occurrence of the disease in some of those exposed and its failure to develop in others in like contact with sources of infection.

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JOHN R. YOUNG, PIONEER AMERICAN PHYSIOLOGIST<sup>1</sup>

By HOWARD A. KELLY, M. D.

John R. Young, a student at the University of Pennsylvania, submitted, in 1803, for the degree of doctor of medicine, a remarkable thesis entitled, "An Experimental Inquiry into the Principles of Nutrition and the Digestive Process." Allow me to premise my subject with a brief general review of the history of digestion in order that we may do full justice to his claims as we recognize the conditions under which he labored and the obstacles he had to overcome.

In the effort to clarify the mystery enveloping the processes of digestion, many bizarre views have been current from the days of the ancients down to recent times.

An *animistic* doctrine held that an archæus, a mysterious spirit resident in the living organism, was the potent factor in the appropriation of the nutriment from the ingested substances, which being interpreted means, I suppose, that it is a vital process, as inexplicable as life itself.

Another view was that *trituration* and *attrition*, so easily observed in the stomachs of grain-eating birds, did the work. This mechanistic notion, coming down from the days of Erasistratus of Alexandria, met its downfall in a *reductio ad absurdum*, at the hands of Archibald Pitcairn (1652-1713), a Scotch physician and poet, and one of the original members of the Royal College of Physicians of Edinburgh, incorporated in 1681. Naively taking Borelli's estimate of the power developed by the flexor muscles of the thumb, and weighing these, and then weighing the stomach with all the surrounding abdominal muscles and comparing them, he easily reached the astonishing calculation that the available compressing and crushing force of the stomach was over four hundred thousand pounds!

*Putrefaction* was a notion which also held sway for ages. Later, when it had been recognized that putrefaction was a form of fermentation, associated with certain well-defined and observable phenomena, this view seemed more plausible. An acid transformation associated with the production of gases seemed to cover both fermentation and digestion, as far as the latter was known from the post-prandial ejecta both of man and his intimate, the dog.

Borborygmi and eructations and a sour vomitus seemed to prove that the sometimes stormy processes of our subdiaphragmatic kitchen are closely akin to fermentation, and judging by the charnel-house which tens of thousands of people, quite certainly then as now, carried around in their mouths to poison the body, the notion of putrefaction does not seem so preposterous.

Van Helmont (1577-1644), emerging from the mists of the middle ages, was a believer in the archæus as well as in a special spirit resident in the solar plexus which presided over digestion; with this mystic bed-fellow he associated some definite scientific ideas and insisted on the presence of an acid.

Thus we have as a heritage of the conjectural age of medicine, trituration and attrition, and coction, and putrefaction, and fermentation, and maceration (Haller), and emerging last of all, chemical solution, to be spoken of shortly.

But while men mused on these things during 300 years, a series of fundamental discoveries were being made in the anatomy of the digestive organs, laying bare the fact that whole series of ducts and absorbents clustered for some puzzling but surely definite purposes around the mouth and the upper intestinal tract, suggesting insistently to the newly arrived scientific mind some positive relation between their activities and the processes of digestion, and raising questions bound to be answered in time, however entangled at first in a maze of conjecture and crude theories.<sup>2</sup> Chief among these discoveries in order of time were the lacteals by Aselli (1622), the pancreatic duct by Wirsung (1642), the thoracic duct and the *receptaculum chyli* by Pacquet (1651), the intestinal lymphatics and their connection with the thoracic duct (1656), and the parotid duct by Steno (1662).<sup>3</sup>

How well might the fortunate scientists in that golden era have applied to themselves the proverb, "It never rains but it pours."

We may fittingly close the hazy epoch of undisciplined guesses, philosophical contemplation, and ignorance with William Hunter's caustic comment on the school of lucubrationists and ratiocinationists: "Some physiologists will have it that the stomach is a mill, others that it is a fermenting vat; others, again, that it is a stew-pan; but in my view of the matter, it is neither a mill, a fermenting vat nor a stew-pan, but a stomach, gentlemen, a stomach."

Lafayette B. Mendel in a charming tribute to John R. Young,<sup>4</sup> divides the history of the effort to understand the physiology of digestion into three eras. The first may be said to end (and, I think, this is the consensus of all physiologists), with Haller's "Elementa Physiologiæ," published in 1757. Not that Haller discovered any fact relating to digestion, for his own idea was that of a simple *process of solution*, but because he rendered the necessary service of gathering between two boards the various conflicting views for comparison, and because he stood on the threshold of the modern chemical era, when the pregnant clouds were gathering over the thirsty land ready to pour down their refreshing discoveries over a period destined to stretch through the next century and a half.

Commencing with the Haller date, and indeed a little before it, we therefore enter the modern experimental or second era, which is illuminated at the very outset by such names as Réaumur (1683-1757) and Spallanzani (1729-1799), and these two, indeed, ought to be hyphenated, for together, as we

<sup>1</sup> Read before The Johns Hopkins Hospital Historical Club, April 8, 1918.

<sup>2</sup> For further data see an admirable résumé by R. J. Cary, in the Bulletin of The Johns Hopkins Hospital, May, 1916.

<sup>3</sup> Garrison: Hist. of Med., 2d. ed., 1917, pp. 237 and 238.

<sup>4</sup> Popular Science Monthly, February, 1909.





SAMUEL YOUNG, M. D.



JOHN R. YOUNG, M. D.



REVERSE OF MINATURE.



Mr. President,  
and  
Gentlemen,  
When we take a view of anatomy, I think, we find that all are subject to a decay—now is man an exception from this, they certainly are not. There are different kinds of his body are sufficient proofs of this general proposition. As a whole is therefore continually young in the body it becomes a principle, absolutely necessary to his life that he have means to counteract this general loss of his system—these are the taking off of food and converting it into a nutritious fluid, so that it may be distributed to the several parts of the body, to repair this general loss. As is known, there wanting in his constitution or himself, as, that he should <sup>that</sup> his food should be converted into meat of it with that strong and unsupportable, <sup>energy</sup>, with a <sup>new</sup> gas, and the gasifying this through to be <sup>new</sup> formed, well preserved.



GRAVE OF JOHN R. YOUNG, HAGERSTOWN.





view them in the perspective of a hundred and fifty years, they blazed a path into the unknown which every investigator has of necessity followed from that day to this.

Mendel's third stadium covers the period of the chemistry of digestion. Hence it is naturally coincident with the rise of modern chemistry, and may be said to begin with the year 1800, and, I would claim, with the work of our hero, John R. Young, of Maryland. More precisely, this era blazoned out with the discovery of free hydrochloric acid in the gastric juice in 1824 by Prout (1785-1850), right after which came the great American work of William Beaumont in 1833, who, living from 1785 to 1853, experimented upon Alexis St. Martin, "the man with the lid on his stomach" through which the processes and the steps of digestion were conveniently investigated in some 238 experiments.

In order to advance more specifically my claims for John R. Young, I must at least epitomize the work of Réaumur and Spallanzani just mentioned. Cary calls the year 1752 a "red-letter year" in the history of digestion, as it was in that year that Réaumur published two treatises on the "Digestion of Birds," the first dealing with the digestion of grain-eating birds with a gizzard, a stout, muscular stomach. Food was put in metal tubes open at the ends, except for a wire grating, which kept the food but did not exclude the gastric fluids; as the food remained unchanged he concluded that the gizzard contained no solvent fluid capable of digesting the aliment. His second memoir dealt with carnivorous birds having a membranous stomach. Here he found that digestion was effected by a gastric fluid, some of which he secured by putting sponges in his tubes; when these were ejected he squeezed out an opalescent, salty, rather sour fluid, which used as an artificial digestant resisted putrefaction.

Spallanzani reviewed Réaumur's work, confirmed his findings, and greatly enlarged its scope. His way of experimenting was to introduce perforated tubes into the stomach, fastened with a wire around the neck of the animal, so that he could conveniently pull the tube out from time to time as he noted the steps of digestion. While testing a great variety of aliments in tubes, he, also, himself swallowed thin linen bags containing food, which he secured for investigation after their passage *per anum*. He also obtained gastric liquor by forcing himself to vomit before breakfast.

"We owe thus to Spallanzani," says Cary, "after Réaumur, the definite experimental proof of the solvent power of the gastric juice upon the various constituents of food, but he was unable to go much beyond this, because he failed to recognize its acid character. He, however, conclusively disproved the older theories of digestion, especially that of trituration, putrefaction, fermentation and maceration." Spallanzani's theory was that of a chemical solution.

The first English experimenter on these fruitful lines appears to have been Stevens of Edinburgh, who, in 1777, wrote a dissertation entitled "De Alimentorum Concoctione."

Great and fundamental as was the value of the observations of Réaumur and Spallanzani, still greater was the fact that they established the absolute necessity of experimental methods

in investigating digestive processes. In doing this they lighted a torch never to be extinguished.

In striking contrast, and so forming a happy setting to his pupil's work, is the thesis of Benjamin Rush, Young's pre-eminent teacher in medicine, which by a happy coincidence had been devoted to identically the same topic 35 years before, and offered for his doctorate in the University of Edinburgh. Its title is "*Dissertatio Physica Inauguralis De Coctione Ciborum in Ventriculo.*" Rush, too, selected an illuminating motto from Verulam (Bacon), "*Omnino Scientia ex naturae lumine petenda, non ex antiquitatis obscuritate. Nec refert quid factum fuerit; illud videndum quid fieri possit.*" The first full-page dedication is to Benjamin Franklin, ambassador to Britain.

Rush begins his dissertation as to the nature and functions of the gastric juice ("*succus gastricus*"), by complaining, "*Dolendum est liquorem gastricum in ventriculo adeo sepultum esse, ut experimentis nostris subjici recuset.*" Réaumur's work was clearly not known to him.

Rush then goes on to state that, as far as conjecture can decide, this *succus* is a thin fluid almost of the same nature as saliva, and that it acts vicariously with the saliva. Pigs, for example, which have little saliva, have an abundance of gastric juice. Rush discusses the question of an acid ferment, suggested by van Helmont, and disposes of it, stating that his experiment (given at the end) proves that it is not necessary that an acid ferment should ever be present in the stomach. He and his friend, William Penny, were wont, with commendable zeal, to throw up their meals for test purposes. Rush uses these words, concluding that the "coctio" of the food in the stomach is a process of fermentation "*Spēctānda nunc sunt phaenomena coctionis in ventriculo, quae consentire phaenomenis fermentationis miro modo videntur. In omni mole ferente observantur inflatio, extricatio aeris, et mutatio integra molis fermentis. Sed haec omnia nobis coctio ciborum in ventriculo exhibet.*" Rush ends with thanks to his master, William Cullen, who suggested his subject, addressing him, "*Vale egregium academiae decus.*"

*Coctio* clearly means the act of digestion in whatever way effected, and is a generic and not a specific term.

Benjamin Rush was easily the master mind in medicine in his day, and his title to be called the modern Hippocrates, and the American Sydenham, was hardly then disputed; but I venture to suggest that he appears in this thesis, as in the work he was destined to do through his following maturer decades, rather as the highest expression of the wisdom already attained than as a pathfinder; he had no genius, no premonitions, and flashed no light into the future.

How little did Rush realize that in that class of 1803 there sat on the benches a country boy from Western Maryland who had a certain rare quality, lacking in himself and in his eminent colleagues, an imagination and a spirit of investigation and persistence, tempered by sound judgment, for which the world is ever waiting; a spark of the same fire which burned in the breast of Vesalius, and of Harvey, and in Réaumur and Spallanzani. Rush had his unquestioned merits,

and holds his accredited place in the evolution of medicine in our country, but Young's name will shine with an ever brighter luster, as the one who first effectively introduced and patiently followed out in this country the modern laboratory methods. Young was our first real scientist in the field of medicine, and was the first to take the fundamental step of demonstrating that the gastric juice is an acid, with solvent, anti-putrefactive properties. Van Helmont had noted the acid long before but it had been forgotten; John Hunter had stated it and had then qualified his statement until it had no force; Young made it the subject of his thesis, demonstrating his contention by numerous experiments, and so took this first essential step forward in the study of the chemistry of digestion.

Young showed that the gastric juice had its origin in a gastric secretion, and that it did not arise from any kind of a fermentative process, vinous, acetous or otherwise. He also noted the important fact that the flow of the gastric juice and that of the saliva were synchronous.

Young's thesis was, therefore, notable and marks a distinct advance in the physiology of digestion. He first takes a stand against the teaching of Cullen, all-powerful in his day, who held that food received into the stomach underwent fermentation with the formation of an acid. Young declares, "That an acetous fermentation takes place in the human stomach in a healthy state, we entirely reject."

Young was peculiarly favored by our North American fauna, for he made his experiments on our big bull-frog, then called *rana ocellata*, whose large esophagus enabled him to insert a *rana pipiens* into its stomach with a thread tied to its leg. He pulled the small frog out at intervals and noted the steps and rapidity of digestion and, disputing the theory of putrefaction, remarked that there was no odor of decomposition.

He introduced a calculus into the frog's stomach and found it gradually dissolved, and recommended this method of treating calculi in the human bladder (as others had done before him) by lading juice out of a frog's stomach with a teaspoon and putting it into the bladder. He put beans, peas, wheat and bread into the frog's stomach and found that in 30 hours the beans, peas, and wheat were not in the least acted upon, but that the bread bag was empty; but when the cereals were crushed he found that they were digested.

He then deals at greater length with the question of fermentation in the stomach, and investigates the three kinds, "vinous, acetous, and putrefactive." An accommodating friend took a meal of sugar and regurgitated it several hours afterwards, when no vinous fermentation was found.

Young himself dined on "chicken pye," and irritated the fauces so as to eject the "pye"; here also he found no acetous change after further warming the ejecta for nine hours. That the acid in the stomach does not come from fermentation, he proved by putting litmus in the stomach of the frog, as well as by removing and examining the food before any fermentative process could have taken place.

Of the experiment on himself, Young says: "I took some meat on an empty stomach; in half an hour afterwards, by irritating my fauces, the meat was thrown up, and with it some

gastric fluid: upon being tested, an acid was very evidently present. Here no one can suppose the acid was to be referred to the meat. We have little hesitation, therefore, in saying that the acid so constantly found in the stomach of man and, probably, almost all animals, is to be referred to their gastric fluid. Having thus, we hope, traced the acid of the stomach to its proper origin, we next attempted to ascertain its nature by chemical tests. Mr. Mitchell being in good health, and having the power to ruminate, frequently threw up the contents of his stomach for me; which being filtered, a transparent and acid fluid was obtained, on which the following experiment was performed: To a portion of this fluid, acetate of lead was added, a white precipitation immediately took place; this being washed, muriatic acid was added, which decomposed it, a very white powder remaining at the bottom, and a fluid above, etc." His conclusion was that he was dealing with phosphoric acid. What a pity that he did not recognize the fact that the very acid he held in his hand, as he added it to the fluid was the acid he sought, thus placing another great discovery to his credit!

In the course of these experiments Young emptied the stomachs of snakes, as well as of frogs, after feeding them on various materials—flesh, bones, teeth, vegetables and cereals.

He explains the process of digestion as follows: "We would therefore explain this process in a few words. Aliment is dissolved by the gastric menstruum; it then passes into the duodenum and meets with bile and pancreatic liquor; after being united with these, a heterogeneous mass is formed called chyme, and from this the lacteals secrete chyle."

He concluded that the tissues absorbing the chyme must play a vital part in the process, and not merely act as absorbents, because the fluid found in the lacteal vessels was always the same to taste, whatever might be the character of the food partaken. He notes in this connection that a patient of Dr. Wistar's lived for many weeks on rectal enemata alone, where bile and gastric juice and pancreatic liquors could not have assisted in the process of absorption.

Mendel adds this comment: "One hundred years later the obscure importance of the absorbing alimentary tract must still be emphasized. In the words of a popular text-book, the energy that controls absorption resides in the wall of the intestine, presumably in the epithelial cells and constitutes a special form of imbibition which is not yet understood. Thus the dignity of the living structures still remains unchallenged."

Young's work was done in a simple, unpretentious effort to discover the secrets of nature by going direct into her house and asking questions. He disposed of the excoagitated imaginary hypotheses of his predecessors and left his subject on the simple basis of established fact. He was the first in this country to take the necessary steps in an entirely new direction, leaving it to his followers to advance step by step, following no other general methods than those used by himself. He was both a pathfinder and a sign-post; he cried out, "Come, stand here; this is the solid ground," and he pointed out the direction to subsequent progress.



Young was the very first American medical man to enter the new field of fruitful experimentation, and to bring home his own sheaf for the garner. With prophetic foresight he takes his motto for the title-page of his thesis from the great Frenchman, the father of modern chemistry, himself an experimenter in physiology, Lavoisier, who declared: "We ought in every instance to submit our reasoning to the test of experiment and never to search for truth but by the natural road of experiment and observation." It was the new spirit of a new age which we of English stock like to trace to Bacon, who laid down the maxim, cited by Professor Mendel, "*Non fingendum aut excogitandum, sed quid natura faciat observandum*," which I venture to render after a liberal fashion.

Long and weary is the way of ratiocination.  
Nothing fruitful ever comes from tedious incubation.  
Nature's ways are only found by patient observation.

#### WHAT YOUNG DID FOR DIGESTION

- (1) He did away with the theories of innate heat and vital spirits as the essential factors in the act.
- (2) He did away with the notion that digestion was essentially a process of trituration, fermentation, or putrefaction.
- (3) He showed that it was effected by an acid which he attempted to analyze, and concluded that it was phosphoric acid.
- (4) He experimented on animals and on men (himself and a friend).
- (5) He secured pure gastric juice and experimented with it *in vitro*.
- (6) He showed that the acid gastric juice checked putrefaction.
- (7) He drew the inference that dyspeptics ought not to dilute the gastric juice with water.

Young has been a most mysterious figure in American medicine, and until now nothing has been known about him, aside from the fact that he went from Hagerstown to the University of Pennsylvania, where he studied medicine, and that he wrote a remarkable thesis; after which he disappeared from sight as completely as if the earth had swallowed him. Even the significance of the middle letter of his name has not been known.

Let me present categorically the hitherto known facts: (1) His valuable thesis on digestion; (2) his name, known in part; (3) the place of his birth (his own town has completely forgotten him); (4) the year of his graduation, after which he disappeared into oblivion.

I now give the results of some investigations I have been making for the past year.

John Richardson Young (let me announce his full name given for the first time in public since his death 114 years ago) was born in Hagerstown, then called Elizabeth-Town. He was the son of Samuel and Ann Richardson Young. His mother died in 1791, at the age of 31, when her son was nine years old, and at his death, thirteen years later, he was laid beside her in the old St. John's burying-ground on Mulberry Street at Hagerstown.

The father, Dr. Samuel Young, was a native of Ireland, a graduate of Trinity College, Dublin, and received his medical education in Edinburgh; he came to this country before the Revolution, and "attained a high position as a physician and a good man."

John Richardson Young was graduated from Princeton University (then the College of New Jersey) in 1799, when he was seventeen and, while there, was a member of the Cliosophic Literary Society.

The study of medicine was begun with his father, from whom he received, as he says in the dedication to his graduation thesis, his "first principles of medicine." The affectionate relation between father and son is shown in other instances, an intimate one being the purchase of a watch made in London in 1804, and given to his son the same year, the year after his graduation, several months after he had joined in practice with his father, and the year of his death.<sup>5</sup>

John R. Young continued his medical education at the University of Pennsylvania, arriving in Philadelphia "Sunday 7th of November, 1802," as a small note-book records in his own hand-writing. He graduated on June 9, 1803, with the thesis which is his title to fame.

Instructors in the medical part of the University while John R. Young was a student were: Dr. William Shippen, anatomy, surgery, midwifery, with Dr. Caspar Wistar, adjunct; Dr. Benjamin Rush, institutes of medicine and clinical medicine; Dr. James Woodhouse, chemistry; Dr. Benjamin Smith Barton, materia medica, botany, and natural history. Dr. Rush at this time was attending also to the duties of the chair of theory and practice of medicine, made vacant by the death of Dr. Adam Kuhn, to which chair Rush was regularly appointed in 1805.

John Andrews, D.D., provost *pro tem.* at the time of Young's graduation, was also a Marylander, born in Cecil County in 1746; he was ordained a clergyman in the Church of England in 1767 in London, England, was a missionary at Lewes, Delaware, and received his degree of Doctor of Divinity from the newly-established Washington College in Maryland in 1785. He was headmaster of the Academy of the Protestant Episcopal Church of Philadelphia from 1785-1789, and in this latter year was made professor of moral philosophy in the restored College of Philadelphia. In his provostship he succeeded Dr. McDowell from 1810 to 1813.

There were 15 members of Young's class, one of whom, John Stevenson Mitchell, of Pennsylvania, was probably the "Mr. Mitchell" who lent himself so obligingly to Young's experiments.

While a student at the University of Pennsylvania, Young fell under the special notice of Dr. Benjamin Smith Barton,

<sup>5</sup> This watch is now owned by Mr. T. Elliott Patterson of Philadelphia, who carries it, and who tells me that it keeps correct time. Mr. Patterson, who was present at the reading of the Young paper before The Johns Hopkins Hospital Historical Club, exhibited the watch.

who became his friend as he was his teacher; to him, also, Young dedicates his thesis.

Young's thesis was published by Eaken and Mecum, Philadelphia, 1803. This edition is rare; a copy is in the Library of the Surgeon-General at Washington, and the copy which belonged to Benjamin Rush is in the Ridgway Branch of the Philadelphia Library.

The work is contained, also, in Caldwell's "Medical Theses," 1805, which can be seen at the library of the Surgeon-General. There is also a copy in the Medical and Chirurgical Library, Baltimore.

John R. Young found his professional billet awaiting him on graduating in June, as is evident from an advertisement July 13, 1803, in the *Maryland Herald* and *Elizabeth-Town Weekly Advertiser*.

#### NOTICE

Having taken my son, Doctor John R. Young, as a partner in the practice of physic; all those indebted to me are therefore requested to settle up their accounts to this date, July 13, 1803.

(Signed) SAMUEL YOUNG.

John R. Young was one of the first contributors to Barton's *Philadelphia Medical and Physical Journal*, and his article, appearing in the first volume, on a "Case of Tetanus Cured by Mercury," bears the date March 29, 1804, but the publication did not appear until the autumn, several months after Young's death, and Barton in a footnote says, "Some account of this truly ingenious and amiable young man will be given in a future number of this Journal." This sketch, however, never appeared.

In the same volume of the *Journal* (p. 145) is an extract from a letter by Young recording his use of "Saccharum Saturni in cases of uterine hemorrhage with complete success." This letter has the same date, March 29, 1804.

An unpublished manuscript written by Young has been found among his effects and forms an interesting addition to his writings. The paper is a clear, simply-worded exposition of digestion, evidently prepared to be read before a mixed audience and before his own work in that subject had been broached. The manuscript is neatly written and bears corrections in several places in another hand, probably that of his father, Dr. Samuel Young.

Young was one of the founders of the American Linnean Society, of which Benjamin Smith Barton was president, and was a member of the Philadelphia Medical Society.

There is one more brief, sad item to be added about this earnest young physician: it is to be found in *The Maryland Herald and Hagers-Town Weekly Advertiser* of June 13, 1804, just 11 months later than the former notice: "Departed this transitory life on the 8th instant in the 22d year of his age, John R. Young, M. D., of this Town, after a long and tedious illness." Following this are two poems laudatory of the virtues of the departed; one is signed "Corydon," and the other "Erigena."

On a beautiful spring day, recently, I visited the grave of John Richardson Young in the old St. John's churchyard. A

fine slab of sandstone marks his resting-place, inscribed with this legend:

IN MEMORY  
OF

JOHN R. YOUNG M. D.  
WHO DEPARTED THIS LIFE  
ON THE 8TH DAY OF JUNE 1804  
IN THE 22d YEAR OF HIS AGE

"Nec prosumus cunctis quae prosumus omnibus artes"

Pause stranger on this sacred spot  
Here give to worth a parting sigh  
So may thy grave be ne'er forgot  
When the lorn stranger passes by.

The grave of the father is separated from that of his son by the graves of two sisters of John R. Young, who died at the ages of 21 and 30, respectively. He lived 34 years after the death of his gifted son, and was 108 years old when he died in 1838, as attested by his gravestone.

From Hagerstown I journeyed across the mountains to the little town of McConnellsburg, which is near "Brookside," the old homestead of the Pattersons, beautifully situated in a mountainous basin in Fulton County, the wildest part of Southern Pennsylvania. Here live Miss Bessie Bell Patterson and her two brothers, William Calvin and John Lind Patterson, whose mother, Mrs. Isabella Milligan Patterson, was the second cousin of our John R. Young.

In this attractive mountain home I saw an exquisite miniature of John R. Young, painted on ivory by Peale, and an oil portrait of old Dr. Samuel Young.

The portrait of John R. Young shows a youth in early manhood with an oval face, curling brown hair coming down over the forehead, blue serious eyes, dark, finely-marked brows; neither mustache nor beard is worn; the face reveals both character and intellect. The reverse of the miniature bears two gold bands with rich blue glass between, and in the center is woven the chestnut hair of John R. Young, with the delicately wrought intertwined gold initials J. R. Y.

Old Dr. Samuel Young's life-size bust, at the age of 74, shows him tall and slim, with sloping shoulders. The face is that of an old man with scant gray hair, blue eyes, thin lips, compressed, determined mouth, and fine intellectual face. The portrait was painted by J. Frymier, three months after the son's death.

There is a family tradition that John R. Young as well as his two sisters died of tuberculosis. Dr. H. B. Jacobs suggests that the mother, dying at the early age of 31, may have had the same disease and have transmitted it to her children.

I have ventured to draw at some length on the various memoranda which have grouped themselves about the name of John R. Young, as but a just tribute to a young man of great promise in the early history of American medicine. After the lapse of 114 years we can well afford to honor his memory not only for his great achievement, but as an expression of thankfulness for the spirit which animated him—that rare spirit which alone has been the beacon light of our profession as it has groped its way out of Cimmerian darkness into the light of to-day.

He first caught the lighted torch, flashed it out into the darkness and passed it on to Beaumont, who sent it on down from hand to hand, through the century, renewed and nourished by each zealous hand that grasped it until its brilliant, steady glow illuminates the whole land.

In the preparation of this paper personal communications have been received from Miss Bessie Bell Patterson; Mr. T. Elliott Patterson; Dr. Ewing Jordan; Judge T. J. C. Williams; Dr. John McPherson Scott; Miss Mary L. Titcomb, librarian, Washington County Public Library; Mrs. O. H. W. Hunter, Hagerstown.

To Dr. Jordan I am particularly indebted for supplying the middle name of John R. Young, and for putting me in touch with the living members of the Young family.

The Presbyterian Church Records (by the courtesy of the Rev. J. Russell Garr) and the Court-House Records (by the courtesy of Mr. Thomas E. Hilliard, register of wills, and Mr. Edward Oswald, clerk of the court of Hagerstown) were consulted; and the following books besides those named in the bibliography: Catalogue University of Pennsylvania with an Historical Sketch, 1836; Scharf's History of Western Maryland; Williams' History of Washington County; Cordell's Medical Annals of Maryland.

Some of the most valuable data I have been able to secure have come into my hands through the indefatigable labors of Miss Harriet Blogg, who has followed with profit some exceed-

ingly exiguous clues, and who has in addition visited Hagerstown, held numerous interviews, and has inspected and secured a copy of the will of old Dr. Samuel Young.

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## THE BLOOD PRESSURE IN AMYLOID DISEASE OF THE KIDNEY

By K. HIROSE

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Since the time of Rokitsansky so many have studied the influence of amyloid disease of the kidney upon the blood tension that it might appear that little remained to be done. Nevertheless, at the suggestion of Dr. Welch, the following attempt has been made to ascertain, (1) whether amyloid ever occurs in the kidney without nephritis, (2) what types of nephritis are associated with amyloid, and (3) what changes in the blood pressure and in the condition of the heart and arteries accompany amyloid disease of the kidney.

#### HISTORICAL SURVEY

Rokitsansky was the first to recognize amyloid disease of the kidney (1842) and distinguished it under the name *Speckniere* from other forms of Bright's disease. Virchow, who studied the chemical peculiarities of the amyloid substance, also separated as belonging to a third form of Bright's disease those cases in which the kidneys contained amyloid. Weigert tried to differentiate several forms of amyloid disease and found that, although there are a few cases in which the amyloid exists in the arteries without other change, there is generally a profound modification of the kidney substance. The most common form is the so-called large white kidney. Bartels also noted the frequent association of amyloid with

chronic parenchymatous nephritis, although he found it only rarely with contracted kidneys. Cornil and Ranvier state that there is always an associated parenchymatous nephritis. Wagner divides amyloid disease of the kidney into four forms characterized by the presence of: (1) Slight amyloid of the cortex and medulla without change in the epithelium or stroma, (2) slight amyloid with fatty degeneration of the epithelium but with normal stroma, (3) amyloid with fresh interstitial changes in the kidney, and (4) the amyloid contracted kidney. Grainger Stewart divides Bright's disease into three forms, of which one is the amyloid form, and recognizes periods in its development: (1) The period in which there are practically no macroscopic changes, (2) the period of swelling, and (3) the period of contraction which may become extreme.

Charcot, Rosenstein, Leyden, Aufrecht, Litten and Raubitschek express essentially similar views.

As to the condition of the heart and the state of the blood pressure in amyloid disease of the kidney, the opinions of writers upon this subject are almost in agreement.

Weigert and Bartels find no enlargement of the heart and no increase in blood pressure, while Wagner and Rosenstein state that hypertrophy of the left ventricle may appear rarely in as-



sociation with amyloid kidneys and then only when there is an advanced contraction of the kidney. Raubitschek found no hypertrophy of the ventricle in cases of pure amyloid disease of the kidney and T. C. Janeway agrees with this view. Geisböck, Buttermann, Hensen, Hayaski and others report cases of amyloid disease involving the kidneys, with subnormal blood pressure.

It is evident from the foregoing that while the presence of amyloid in the kidneys is associated with various forms of nephritis, the impression prevails that there is no hypertrophy of the heart and no increase of blood pressure.

#### MATERIAL

Of 87 cases of amyloid disease collected in the pathological departments of The Johns Hopkins University and Bay View hospitals, 59 were selected which showed definite amyloid changes in the kidneys. Sections were stained by the various well-known methods and the cases analyzed and tabulated to show the condition of the kidneys, heart and other organs as well as the state of the blood pressure and other clinical conditions. These tables are, however, so extensive as to make their publication impossible, and we have been content with a summary of the results of the analysis.

#### PATHOLOGICAL ANATOMY

The changes in the kidneys are extremely variable. Amyloid is found in the glomeruli, in the other blood vessels of the kidney and in the walls of the tubules.

The glomeruli were practically always involved. There was one case, however, showing amyloid in the spleen, liver and other arteries of the kidney in which the glomeruli were free. Such cases have been reported by many authors (Schmitz, Rosenstein, Kyber, Litten, *et al.*), while Kyber also reports one in which amyloid was found in the glomeruli only.

The remaining blood vessels were affected in all but 13 cases, while the walls of the tubules showed amyloid less often. There is marked variation in the quantity of amyloid deposited in the various parts of the blood vessels, a fact which has long since been recognized.

The epithelium of the tubules showed changes in practically all the cases, appearing almost normal in only one instance, in which, however, there were rather extensive scars. In general, the tubules were dilated with swollen granules or fatty epithelium or were lined with much-flattened cells. Granular and hyaline casts and epithelial debris were common.

The interstitial tissue was increased in amount and infiltrated with wandering cells in all but 10 cases which showed no changes. In 22 cases the stroma was especially increased, diffusely in some cases, but in others particularly in the cortex round the glomeruli.

It is evident from this that in every case there was at least a trace of nephritis with degenerative changes in the epithelium of the tubules and scarring of the most affected areas.

The question arises as to the relation between the amyloid deposit and the other changes in the kidneys, and it is most important to know if possible whether both were caused by the same etiological factor or whether the formation of amyloid preceded and caused the nephritis, or the nephritis the amyloid.

That the succession of events is not the same in all cases is clear from the following facts. In the amyloid kidney there is sometimes extreme fatty degeneration of the epithelium with very slight amyloid change or, on the contrary, extreme amyloid change with very slight alteration of the parenchyma of the kidney. Indeed there are cases in which, in the presence of amyloid changes in spleen and liver, the kidneys show parenchymatous changes only.

On the whole, there seems to be little reason to believe that the amyloid itself can play any part in causing the nephritis. Rather it is possible that the disease which causes the production of the amyloid is also capable of producing changes in the kidney substance. Nevertheless, the fact that one may find kidneys in an advanced stage of contraction and scarring in which amyloid is beginning to appear seems to show that the amyloid may be developed secondarily.

#### BLOOD PRESSURE

It is generally stated that in contrast with the cases of nephritis uncomplicated by amyloid, the blood pressure in cases of nephritis with amyloid is not increased. This appears to be supported in this series, although there are six cases in which the heart weighed over 400 grams. Unfortunately the blood pressure was not exactly measured in these, but is merely noted as "good tension" or "fair tension," except in one case, in which the heart weighed 440 grams and in which the systolic pressure was 120 mm. In 13 other cases in which the measurements of the pressure were made the heart did not exceed 300 grams in weight and was generally below 250 grams. In these the systolic pressure ranged from 90 to 120 mm. Hg. and the diastolic from 60 to 90 mm.

It might be thought that the cases in which the heart was enlarged were especially those in which the development of a chronic nephritis with contracted kidney had preceded the appearance of amyloid and therefore a survey of the weight of the kidneys might be of interest. In 40 cases the kidneys weighed more than 300 grams; while in nine only did they fall below this weight. In the cases in which the heart weighed over 400 grams, the kidneys weighed 400, 500, 550 and 300 grams. There were two other cases in which there were small granular kidneys. Thus the great majority of the kidneys in which amyloid is found are distinctly larger than normal, and even in those cases in which the heart is enlarged there were only two cases in which the kidneys had the character of contracted kidneys. Of the 11 cases in which the combined weight of the kidneys was below 300 grams, only one presented a heart of weight greater than 350 grams.

The reason for the absence of cardiac hypertrophy and of heightened blood pressure in cases in which there is amyloid disease of the kidney is quite unknown. Geisböck found that

in most cases of tuberculosis the blood pressure is low, and Bouveret emphasizes the fact that hypertrophy of the heart may be lacking in chronic nephritis where there is also senility, tuberculosis or other cause of cachexia. The suggestion that the low blood tension may depend upon a coincident extensive destruction of the adrenal by the deposit of amyloid is not convincing, since it is by no means proven that the high blood pressure in nephritis is brought about by the adrenal secretion. In this series, 12 cases showed involvement of the adrenals, but of these one at least showed a high blood pressure and another a great hypertrophy of the heart.

Edema appears to be a not uncommon symptom of amyloid disease and was present in 21 of these cases. Rosenstein found it in 61 of 72 cases, Fehr in 98 of 152 cases, while Grainger Stewart found it in only 6 of 100 cases.

From the analysis of the cases it was found that tuberculosis occurred in 28 and syphilis in 22. Other chronic infections were also found, often in connection with these, so that the cause of amyloid disease cannot be regarded as simple.

Thirty-two cases were male and 27 female. Fehr reports 89 cases in males and 63 in females.

With regard to age, it was found that most of the cases died in the third decade, as shown in the following table:

	Age- 1-10	11-20	21-30	31-40	41-50	51-60	61-70
Dickenson 61 cases.....	3	11	21	10	10	3	3
Fehr 144 cases .....	6	24	43	36	23	7	7
Hennings 76 cases .....	3	19	21	20	7	3	2
Rosenstein 32 cases ....	0	1	11	5	9	4	2
Hirose 59 cases .....	0	3	18	12	15	8	3

The excess of deaths with amyloid diseases in the third decade is probably due to the fact that tuberculosis is so common in persons of that age.

It is striking that of the 59 cases, 26 were negroes, in spite of the fact that more whites than negroes were treated in the hospital. Lambert thinks that the influence of race upon the incidence of amyloid is negligible. In oriental countries, especially in Japan, it has been thought rare, but recently Japanese authors (Katsurada, Miura, Matsuo, Nagayo, Sugai, Tanaka, Tsunoda, Takesaki, Yamagiwa) have reported many cases in which amyloid disease was advanced.

#### SUMMARY

1. In a series of 59 cases the presence of amyloid in the kidneys has always been associated with chronic nephritis. It is impossible to determine whether the nephritis antedated the amyloid or was developed coincidentally with it. In 40 cases in which measurements were given the kidneys were larger than normal, while in nine they were small and granular.

2. In all but one of the 15 cases in which the blood pressure was recorded it was found to be normal or below normal. In the one case in which the systolic pressure was 170 mm., the kidneys were rather large and there was no cardiac hypertrophy.

3. Of the 59 cases, 10 showed cardiac hypertrophy, but only one of these was associated with small granular kidneys, and in none was high arterial tension noted.

It appears from this that even if it be assumed that a persistent nephritis produced cardiac hypertrophy and hypertension, the advent of the amyloid-forming process must have reduced the blood pressure to a low point and may even have caused a retrogression in the size of the heart.

In conclusion, it gives me great pleasure to extend here my heartfelt thanks to Professors Doctors Welch and Winternitz, and to express my sincere appreciation of their keen interest in this study and of their many helpful suggestions and directions. Moreover, I beg to acknowledge my obligation to the physicians in The Johns Hopkins Hospital and Bay View Hospital who have kindly permitted me to publish the clinical histories.

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# BULLETIN

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## THE SINUS-SPUD

By WILLIAM S. HALSTED, M.D.

Many times for the past 22 years I have been reminded at the operating table and in the wards of a certain remarkable case to which I have frequently referred in my clinics as typifying in an unusual and extreme fashion nature's process of local protection and repair in her combat with infection. In this period I have seen three other cases—the last one only a year ago—which, in the essential features, were almost identical with the first.

CASE 1.—About 22 years ago a distinguished physician from a neighboring city consulted me in regard to a tumor which he and his colleagues believed to be a cancer of the rectum. Just before leaving home he made his will, believing that his life would soon be terminated either by operation or by the disease. He was admitted to The Johns Hopkins Hospital and the story told by the notes of his case is as follows:

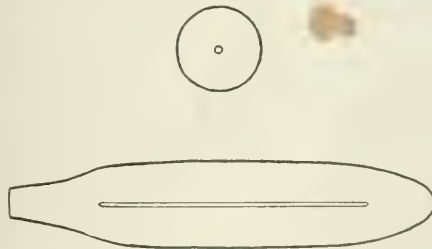
Surg. No. 4949. Male, æt. 59. Admitted to The Johns Hopkins Hospital December 20, 1895. Discharged January 4, 1896.

The patient states that he first observed a tumor in his perineum about two months ago. Occasionally he has noted neuralgic-like pains in this region.

In the perineum, 1 cm. to the left of the mid-line and 2 cm. posterior to the scroto-perineal junction, the tip of a hard teat-like mass can be felt. The tumor can be traced from this point across the median line to the right side and thence backward toward the rectum and bulbo-membranous urethra. The anterior, more superficial, part lies just beneath the skin and is freely movable; the central portion is less movable, and the posterior extremity is quite fixed and deep. The mass is hard and insensitive, except on rough manipulation. Rectal examination negative.

Operation December 21, 1895 (Dr. Halsted).—A straight incision through skin and fat exposed the nearly circumscribed tumor

which was composed solely of fibrous tissue. In its center was a sinus which, traced with a fine probe, was found to be about 7 cm. long. It was blind at both ends. (*Vid.* Figure.) Posteriorly the tumor terminated on the aponeurosis of the levator ani muscle about at the junction of the transversus perinei and erector penis muscles. In the course of the dissection the bulbo-membranous



APPROXIMATE DIMENSIONS OF THE SINUS-SPUD AND ITS CENTRAL CANAL IN CASE 1: LONGITUDINAL AND TRANSVERSE SECTIONS.

urethra was exposed, and the fact established that the sinus had no communication either with it or with the rectum. The wound was left unclosed with the idea that any overlooked communication with the rectum or urethra might be promptly detected. But no fistula resulted.

CASE 2.—The second case of what I have termed sinus-finger or sinus-spud was also a private patient at The Johns Hopkins Hospital, but, unfortunately, I have not been able to find the history and cannot recall the name of this patient. The pertinent facts, however, I remember distinctly.

The patient, a male, æt. about 35, was short in stature, rather emaciated and of sallow complexion. He complained of a dull pain in the right iliac fossa, but denied having had attacks suggestive of appendicitis. A very hard, rather diffuse but quite nodular mass could be palpated in the region of the appendix. I expressed to the patient's friends the opinion that he probably had a cancer, either of the cecum or of the vermiform appendix, and advised exploration. The patient had a horror of the knife and refused to be operated upon. In the course of a few months he again presented himself for examination. The mass was definitely smaller and perhaps harder; it was only slightly if at all tender and caused very little discomfort. There seemed to be considerable improvement in the patient's general condition. Withdrawing my diagnosis of cancer I urged exploration, believing that the appendix was responsible for the trouble. The patient again declined operation, but returned in the course of, perhaps, six or eight months for observation. The mass diminished slowly in size until at the end of about one year it resembled in form the tip of a finger. Forcible palpation of the little spud caused no pain. Of the ultimate fate of the mass or of the patient I know, unfortunately, nothing, but I am quite sure that this was another instance of a fine sinus surrounded by a finger-like bud of connective tissue.

CASE 3.—Surg. No. 11187. Male, æt. 48. Admitted to The Johns Hopkins Hospital November 16, 1900. In May, 1899, the patient had been treated for fistula in ano.

About two weeks before admission he had had quite severe pain "back of the rectum." He stated that there had been slight swelling and faint redness somewhere in this region, but he had not observed blood or pus or anything abnormal in the stools. The pain was not increased at defecation.

Examination: In the mid-line, just posterior to the scrotum is a hard, circumscribed, quite freely movable and slightly tender mass. Nearer the anal margin along the raphe is a little abnormally resistant and slightly reddened area. The two swellings seem to be connected by a narrow strip of indurated tissue. "Dr. Halsted described the prominence in the anterior part of the perineum as a finger-like mass connected with the posterior area of induration by a pencil-like process."

*Operation November 17, 1900.*—Complete excision of the areas of induration. The excised mass consisted solely of fibrous tissue surrounding a sinus tract. In the anterior finger-like portion the sinus was very fine and its connective-tissue capsule remarkably thick. Posteriorly the sinus was wider and its fibrous envelope much thinner. There were some tiny pockets of pus and necrotic tissue in the posterior portions of the sinus. Careful search was made for a fistulous connection with the rectum or urethra, but none was found.

Observations made by the patient during urination and defecation failed to detect escape of gas or fluid or foreign matter into the wound. There was no evidence of fistula at the time of discharge from the hospital December 15, 1900. After a little more than a year (February, 1902), however, the patient returned with a perineal fistula, which communicated with the urethra.

CASE 4.—Male, æt. 45, consulted me in May, 1917, for a tumor in his perineum. He stated that he had never had any urethral trouble. Two years previously he had been operated upon for hemorrhoids. About one year after this operation he had begun to be troubled with pain in the perineum.

On examination a hard, smooth, finger-like mass about 5 cm. long and perhaps 1.5 cm. broad was found in the perineal mid-line extending backwards to within 2 cm. of the anal margin. The anterior end of the mass was rounded, definitely circumscribed and not adherent to the skin, which was normal in appearance and texture. Quite forcible manipulation of the finger-like tumor caused no pain, nor did there seem to be any tenderness on deep

pressure. The rectum was examined with negative result. The patient experienced no abnormal sensations at stool or during micturition. The findings altogether were, to the best of my recollection, almost precisely the same as in Cases 1 and 3. I assured the patient that the tumor was not a neoplasm, as had been supposed, and explained to him its nature. Operation was deferred on account of urgent business affairs.

About two months later, July 29, 1917, the patient consulted Dr. Follis because the mass had increased in size and become tender. Dr. Follis, who had assisted me to operate on Case 3, immediately recognized the nature of the trouble and advised excision. For some reason operation was again deferred. On examining the patient three weeks later Dr. Follis noted that the mass had entirely vanished. Incident to its subsidence there had been observed no signs of an abnormal discharge from rectum or urethra and no unusual sensations.

In April of this year (1918) the patient consulted Dr. Follis with reference to another matter and stated incidentally that there had been no return of his perineal trouble.

We may, I think, confidently assume that the nature of the tumors or spuds was the same in the four cases here recorded. In the three perineal cases the pictures were, in every particular, so nearly identical that, presumably, they had also a cause in common. In one instance (Case 3) a urethral fistula developed two years after the excision of the sinus and its fibrous wall. Hence from this we might naturally conclude that a urethral lesion was responsible for all of the perineal spuds, notwithstanding the fact that no one of the three patients could recall having had at any time a urethritis. But this patient (No. 3) had been treated for fistula in ano a year before his perineal tumor appeared, and No. 4 had been operated upon for hemorrhoids. In the two cases operated upon by me (Nos. 1 and 3) we felt we could assert positively that at the time of operation the sinus did not communicate with either rectum or urethra. In both of these cases, furthermore, the sinus did not extend in either direction to the end of the spud. The original urethral or rectal openings must have been very minute and have become closed.

It is, I think, particularly significant that in the three perineal cases the situation of the spud was precisely the same, and the dissection in the two operated cases led to the same spot, viz., to the neighborhood of the bulbo-membranous urethra. If the three cases had been of rectal origin it is extremely unlikely that the rectal perforation would in each have been identically at the same point.

How is the disappearance of the spud in Case 4 to be explained? Did an abscess form and rupture into the urethra, or did the acute inflammatory process sterilize the chronic sinus and thus bring about absorption of the fibrous tissue and its lining? The latter explanation is, I think, the more plausible, for if an abscess had ruptured into the urethra it is likely that there would have been some indication of it either at the time or later. An analogous process is observed occasionally in atheromatous or sebaceous cysts. A wen may disappear after being inflamed; its epithelial lining becomes destroyed and the sac absorbed as a result of the infection. So, too, an empyematous gall-bladder may rapidly shrivel

to a nubbin, and an inflamed appendix to a fibrous cord. Sinus tracts of years standing heal promptly when sterilized. I recall having seen an abscess of the tongue without operation become rapidly converted into a sterile cyst with clear contents.

Correct interpretation of the condition is important, although failure to recognize the nature of the tumor could hardly be disastrous. Faulty diagnosis, however, caused three of the patients great distress.

A finger-shaped, subcutaneous tumor of the perineum, quite free at its tip and with the hardness and elasticity of cartilage, is probably a sinus-spud and may be recognized almost at the first touch of the palpating finger.

Many surgeons undoubtedly will recall transitional forms of sinus-spud—bud-like processes of fibrous tissue of various dimensions enveloping a central sinus communicating with the rectum, urethra or mouth.

## MEDICAL-INDUSTRIAL RELATIONS OF THE WAR<sup>1</sup>

By DAVID L. EDSALL, M. D., Boston

The use now of the word "war" in a title demands that one shall offer some definite line of action, some facts upon which action may be built, or an apology. I fear that I shall leave you with the feeling that the apology is due, for I shall speak of war conditions chiefly as illuminating what we have not done in the past, or what we need to do in the future. But I have not used the word inadvertently or to excite attention, for by this manner of treatment I can still hope to indicate, if I do not specify, the directly medical demands of the moment, for they are those of the future, met as well as may be done by hasty methods; and there are several branches of the problem that are so outstanding that each must be referred to in order merely to picture the scope of the general problem, so that to go into details in all of these would be impossible and I shall rather refer you to more expert sources for details. And besides the distinctively medical problems, which are themselves sufficiently numerous and complicated, one must give at least a little thought and discussion to the world-wide influence that the war has had in arousing or accentuating movements in the management of industry and among industrial workers, movements that will certainly have profound influences and may have tremendous influences upon the world, and not impossibly with singular promptness and directness upon medicine as a profession.

If in a brief time I can give a superficial suggestion of the general relations of medicine to industry, and can combat what I think I may fairly call the common academic aloofness of medicine toward these things, can combat it without desiring to destroy a grateful and healthy conservatism in medicine, and without, of course, wishing to mingle in the bitterness and strife that our minds involuntarily attach to industrial issues—though we nevertheless must sometimes come close to these things—I shall have accomplished my main purpose.

In bringing in one of his pet views in a discussion before the British Medical Association, Clifford Allbutt once announced, "I will now trot out my old jade." Dr. Miller intimated, when he asked me to come here, that I might be permitted to do the same; but I want to dress my old jade in somewhat new trappings—or rather, they are not quite

new but have been on hand for some time and I have tried them on tentatively before, but I was not sure that they appeared to fit the humor of my audience and put them away for a more convincing occasion. I think the war gives this occasion, and I shall make bold to determine whether you do.

I have long ridden a hobby that has the fascination of not only being an amusement, but of possessing both clinical and research interests and also large human interests, relating both to individuals and to groups of people. Industrial disease combines, to an unusual degree, the charm of the study of disease itself, of its etiology, and of the wide human relations of medicine, and it brings one into touch, besides, with an unlimited display of constantly changing technical processes that exhibit the ingenuity and resourcefulness of man to the full. But interesting hobbies, like men themselves, do not stay the same size or shape; they, too, either grow or swell, and this one has changed its appearance to such an extent that one needs to determine which it is doing.

We see its present proportions better if we stop speaking simply of industrial disease, a term inextricably blended in our minds with a few diseases, such as the industrial poisonings that are due specifically and beyond all doubt to industry, and think rather of the general relations of industry to health. We then see at once, that it is no longer a question, as it usually is with us internists, of an occasional patient who has suffered from an occasional severe hazard, our responsibility to whom is covered by ordinary treatment and by the advice to take an occasional dose of salts and keep his mouth clean, or to wear a respirator—which, of course, he will not do—or to change his occupation. Nor is it even covered if we go so far as to take what steps we tactfully can to see that others are protected from the danger.

It becomes at once a question that impinges upon very complex affairs. There has been a definite and increasing new medical demand in recent years in well-organized industry. This is partly due to compensation laws; partly due to clearer recognition of the cost and disorganization resulting from sickness and from the labor turnover that is in large proportion the consequence of sickness or of dissatisfaction with physical conditions of work; partly to the increased demand for labor and the need for stopping waste of that available and of

<sup>1</sup> Read at The Johns Hopkins Hospital Medical Society, March 18, 1918.



using some that would in times of plenty be discarded as unfit; and in large part, I am happy to believe, in consequence of greater enlightenment and humane impulse. It is a demand for men who will know how to keep employees well, how to shield them from the inevitable hazards of industry and to help in doing away with those hazards that are not necessary, how skilfully and speedily to put back at work those that are damaged by them, and how to fit the large group that are, physically, to some degree abnormal to work that they can still successfully do.

Other things even more important to industry are assuming a partly medical nature, hitherto unrecognized. I shall refer briefly to these later. Whatever results may ultimately come from this movement, it is clear that there will be necessary adjustments of medicine to it; for after all industry is the biggest and most powerful thing in the world, and considerable alterations in medicine as a profession would be slight affairs as compared with some of the fundamental changes of which there are even now suggestions in industry. The demands of the war make us see now many things that perhaps had not penetrated our consciousness very clearly before.

Society at large, employers and the working people themselves have in this country done very little about industrial health until recently, but they have in latter years moved much faster than medicine in this matter and would have moved faster still had not the impulse to progress been due chiefly to social and economic influences and but little spurred on in this country by those whose work is health and disease, for it is a fact that medical men have played a comparatively small part in it. It is highly interesting to learn the breadth of what some industries have done and plan to do in this work. To be sure these things need to be far more generally and often better done, but that fact only emphasizes the view that I wish to present and so far as I can see simply indicates that there will be far more done, and the light that the war has given is likely to make progress much more speedy and general. Medical men are evidently needed now who have the kind of knowledge and training to make them fit to aid in managing this extensive, varied and complex matter. There is now developing, as you are well aware, a distinctly new type of doctor—the industrial physician. Few people realize the opportunities for public service that these men have, and still more will have under proper conditions. An unfortunate side of their work in a considerable proportion of the rather limited number of plants where they have been thus far introduced is that in the organization they have been unduly subordinated, especially to a "welfare department", to which they need to be coordinated but not subordinated. And there has at times been in the instructions under which they work so much of "benevolent feudalism," as an able government official put it to me, that they have often not fully gained the confidence and cooperation of the working people. But in large part the fact that they have worked in a subordinate position and under rather rigid instructions has been due to the scarcity of able men of independent character, qualified to do the work and with

comprehension of its important economic relations. They certainly have not been produced in any systematic way through the foresight and aid of educational institutions, but through circumstances and their own initiative; and not many have been able to develop adequately through their own initiative. They are needed now more than ever in maintaining the health of industrial workers, for we have highly dangerous occupations added through the war and they are running under extreme pressure, as are for the most part the usual industries of non-military character that are dangerous. I have had opportunity to offer suggestions to government officials in regard to the preservation of health and efficiency in the workers in those trades, and a great difficulty, the most serious difficulty, perhaps, in planning for the most evident needs in this is not with government authorities or with the most enlightened employers, but in the securing of more men trained to do the work at all well.

How big are opportunities in this work now, and first of all in the trades in which there are definite health hazards?

The importance of this part of the problem may seem too limited to many of you to arouse great interest. Indeed, I have actually had it suggested to me by medical men that to establish at the present time means of preventing even dangerous industrial poisonings is too likely to slow up production and should not be undertaken. As to this latter point, if it were necessary to have many poisonings in order to win the war, we might admit the force of the argument as we admit the need of losing lives in battle. But in industry the shoe is mostly on the other foot. Years ago the manager of one of the largest lead using companies in the country said to me that they were driven to use measures to protect their men from lead poisoning because the character of their product and the reputation of their business were suffering from losing so many skilled workmen temporarily or permanently from poisoning. This is in abstract the true point of view as to production. The most important safeguards usually require no methods or construction that consume a serious amount of time or labor, but rather demand a knowledge of and systematic application of simply applied principles. Certainly England has been under heavy pressure, but because of the need of conserving labor and because of an educated sense of right she, for example, unhesitatingly proceeded to determine, by experimental and other methods, the cause of the remarkable poisoning that was observed to occur from spreading the "dope" in making airplanes, instituted measures to control it and as soon as a substitute for tetrachlorethane was found, even though it was not quite so satisfactory, made the use of the more dangerous "dope" illegal.

As to the scope of the problem, let us consider first its extent in things of such immediate interest as the making and handling of explosives. Dr. Alice Hamilton found about 30,000 people exposed to poisonings in this work at any one time in 1916. But many more were really exposed, in view of the fact that the labor turnover in this work is enormous. With extremely fragmentary sources of information available she was able to collect 2507 cases of poisoning confirmed by

medical diagnoses. The most common of these were poisonings from nitrogen oxide fumes, nitration being an important part in the making of most of these explosives. The main effects of these fumes are much the same as those of the chief gases used in warfare. It is striking to see collected almost 1400 cases of men thus gassed before we were at war and to know that this was only a part of them. Trinitrotoluol poisoning was next in frequency with nearly 700 cases.

Though considerable and though but a fraction of what has actually occurred, what I have mentioned does not make this seem a very large problem in these days of big figures. But in poisonings alone we have to consider many other things not included in Dr. Hamilton's study, things important in war as well as in peace. There are, for instance, so many and such important ways in which our old friend lead is used that there are many more people exposed to it than to all the poisons used in explosives. How many suffer from it we have no way of learning in this country with anything approaching accuracy, though Dr. Hamilton again in earlier studies has given us valuable information. There are many more cases than we usually recognize by our ordinary medical methods, methods which, I may fairly say, scarcely take any account of occupation as a factor in ill-health. At the Massachusetts General Hospital we had, in five years preceding the time when some special attention was given to occupation in relation to health, 146 cases diagnosed as lead poisoning in the wards and outpatient department. In March, 1916, a clinic for the special study of occupational disease was started, with Dr. Wade Wright devoting his entire time to it. Those patients in occupations that are known to be likely to produce disease were sent to that clinic and some special interest was given to discovering all the lead cases among these. In the ensuing year 148 were found, of which 138 were occupational. We are not especially in contact with lead industries and this experience makes it evident that there is a good deal of it about in ordinary medical work when a trained man looks for it, and that a good deal of it is usually overlooked. The problem of poisonings is really a very considerable one. But that is only a little part of the problem of industrial health. We had in that clinic in a year over 5100 patients that had been exposed to some health hazard in industry, and in whose cases it was desirable to determine with some care and by means of trained knowledge whether the occupation had something, large or small, to do with the disturbed health. These hazards ran from sharply definite things like poisonings through the numerous almost equally definite strains to somewhat less clear things like varying exposures to irritating dusts and so on to that rather vague condition "general fatigue," which is hard to determine unless very marked, but nevertheless in its milder or more marked degrees is probably the most common and important industrial cause of inefficiency and ill-health. Surely occupation is a factor quite as worthy of study as alcohol, exposure to infections and various other things that are part of the decalogue of history taking, and it needs training in the principles of comprehending it in order to study it.

Now let us add to this the handicapped—those who are through some disability unable to follow their proper occupations or who do so with more or less peril, or who, disabled early, have never become successful wage-earners. Many of them we know could safely make a good wage and would often be improved physically if trained to a proper occupation. The training we cannot give, but the early supervision of the training and to a considerable extent the choice of a proper occupation are definitely medical problems. But to do this means to know precisely certain principles about the exact nature of individual occupations. No doctor can know the details of all occupations—all individual jobs—nor can any one else. He can, however, know types and acquire ability to judge of the details of others and of their fitness for a disabled individual from descriptions. But aside from a few able industrial physicians how many doctors know enough about jobs to know which handicapped fit which jobs, except for a very few that they have seen, but that are sadly inadequate to meet this situation—such jobs as watchman, elevator man and messenger? Physicians usually have a human interest in the ingenuity of machines and in seeing raw products become finished articles, but I think comparatively few of them often observe *precisely* what the human being at the machine does. Some time ago I spoke to the medical society in a great paper manufacturing town. That afternoon I had been to see certain processes that I was unfamiliar with and among them was the sheet calendering of fine paper, in which the sheets are fed into the rolls by hand with a rapid sharp motion of the hand and wrist, repeated many times at great speed. I asked many of the local physicians that evening if they had seen any neuroses from it. Nearly all knew the process, but scarcely any had noticed exactly what the girls did. However, upon thinking a bit, several remembered that they had seen neuroses and tenosynovitis of the right hand and arm in calenderers.

I recently spent ten days in investigating for the government the affection that occurs in workers in soft stone in association with the use of the pneumatic hammer. The disorder is not at all serious, but it had caused some apprehension among the men and some trade union excitement, and it was feared that the disquiet might spread to other trades now extremely important in war work in which the air hammer is widely used. It was a singularly good example of the importance of observing slight details of the work. It appears practically not to affect the men in these other trades, and this is chiefly because in these other trades a tool, if used with the hammer at all, is often held perpendicularly and is in any case rarely gripped firmly, whereas with the stone workers the tool is used almost constantly, is held in an oblique position and must be grasped very firmly. On such slight differences one can reasonably base a confident opinion that this affection should in no way interfere with the winning of the war.

I have always felt grateful to Sir William Osler for asking me to write certain articles for the original edition of "Modern Medicine," a task for which I felt myself very ill-suited, but which gave me a stimulus without which I should never have learned that a factory is a genial garden to the lover of etiology,

with much fruit on many a tree. It is from this standpoint of etiology that a capable industrial physician sees a factory, and from the standpoint of prevention in the mass and prevention in the susceptible individual. For instance, Dr. Irving Clark, of the Norton Grinding Works in Worcester, tells me that he takes people with hypertension, organic heart disease and various other serious diseases into the work of that factory, which is in large part unusually heavy work, and declines only 3 per cent of the applicants who pass the employment office and are sent to him for physical examination; but he designates carefully what jobs the abnormal shall do, and they are not only not harmed by the work, but are often improved by it. In other plants with less heavy work the number not accepted for physical reasons runs down to one-half of one per cent. Contrast that with the records of physical rejections from our National Army to see what kind of a job this part of the industrial physician's work is—and in the National Army the material is drawn from a group much younger and better cared for than the average of applicants for work. Consider it also in relation to what they have had to do abroad in industry during the war. How valuable there a vast amount of human material has been during the past three years that is ordinarily, to use the common harsh but pregnant term, scrapped.

But how big is the problem of the handicapped? I cannot attempt here to discuss this matter as it relates to the fighting excepting merely to say that while in the war the number involved will of course depend upon the duration and the extent of our participation in it. I have had the privilege of having a slight relation to this problem as it is being prepared for in the surgeon-general's office, and I think that I may safely state that, although the numbers may grow mournfully large, the total of those that will need vocational readjustment owing to actual disability will be decidedly smaller than is often thought, though it may run into many thousands. It is beginning to be recognized that it is a much bigger problem in peace than in war, and that unless the splendid system that is being built up to meet the war conditions is adjusted to and carried over into peace conditions the greater opportunity for service will be lost. Let me justify this seeming paradox. Last year there was an official investigation in Massachusetts of the need of vocational reeducation by the state of those disabled by industrial accidents. The number of persons thus disabled in our state each year appeared to be from 500 to 2000. In Illinois they find the yearly number to be over 2000. Multiply that by 48 states proportionately to their various industrial populations and you have a goodly problem increasing year by year. Add those disabled by non-industrial accidents, by tuberculosis of the joints and by other more or less surgical conditions, and then add poliomyelitis, which in the Cleveland survey of cripples stood next to industrial accidents as a cause of crippling, as that word is commonly used, and the problem swells to more than double. But the medically crippled are in point of fact equally within the problem and adding them makes an enormous accession. The Society for the Prevention and Relief of Heart Disease esti-

mates that there are now in New York City among the school children alone, entirely aside from the adults, 20,000 subjects of heart disease who are bound to be more or less reduced in income and productivity by their disease and most of whom could be much improved economically and often physically by being properly fitted to do suitable work. They consider this the largest economic problem in medicine among those that have not yet been seriously attacked. I think that I do not need to go in detail into all the other important medical causes of disablement.

The problem of the handicapped is one that must be handled in part by others than doctors, and financed probably partly by industry and partly by society at large, but it must be guided in considerable part by doctors and they cannot guide it wisely by depending entirely upon others for the knowledge that is essential to make it either physically or economically a success. In caring for those disabled in war or in peace the medical man should be able to help definitely to decide whether the little details of the jobs under consideration can be performed successfully, and further—what the vocational teacher cannot tell—whether late physical effects of the work consequent upon the handicap may be expected to occur which might render education for the job ultimately fruitless.

Let me now turn to a third subject which, as I have indicated, is a part, but a large part, of what I have discussed earlier. You are aware that from the early days of the war there has been a committee at work in England called the Health of Munition Workers Committee. It is not doing entirely new work, but has greatly expanded and intensified work that had been in progress for some time before. The dominating purpose of this committee now is to aid in putting output, with a limited labor supply and a tremendous demand for munitions and other essentials, at the highest point compatible with an effort expected to be several years in duration. There has been a similar committee in this country since last summer, the Committee on Industrial Fatigue, which is a national defense sub-committee. The United States Public Health Service is intimately cooperating with it and has a body of field workers carrying on studies in factories. I have the privilege of being a member of this committee and I think that I may properly explain a little the purpose of its work and that of the British committee, as there is a tendency to misunderstand their aims. Just as we know that an athletic team may be made highly successful through careful regulation of its food and drink and other factors and especially through trained determination of the effort that it shall put forth, but that the same team goes stale if the effort be overdone, or becomes flabby if it be too little, so does trained study lead to certain quite clear principles and details that are coming to be important now when one wishes to keep industrial workers producing effectively, but avoid having them go stale. There has been a common feeling among employers that any one who is interested in this matter is really interested in shortening hours and is a partisan of labor. As a matter of fact, these committees are not working to shorten hours, but to aid in determining the optimal hours as well as the best



feasible conditions of housing, food, transportation to and from work, general sanitation and other factors in order that fatigue may not reach the point where it interferes with the largest productive capacity. It is undeniable that the studies thus far have often shown that hours should be shorter, but the studies have usually been undertaken purposely in processes where the hours were very long or the work very trying; and, on the other hand, it is true that most workers even, as well as most foremen, managers and employers, have until lately thought rather blindly that the longer the work the greater the output. But there has been a good deal of change in this recently. Many employers have latterly experimented accurately with shortening long hours and nearly always with favorable results. There are, however, under study many other things besides total hours, such as night and day work and the best distribution of these with an individual worker, the length of spells, and the effect of several brief rest periods; and there are partly at hand and partly being developed a variety of methods of determining the existence of fatigue, direct physiological methods, such as Stanley Kent's test of the acuity of vision before and after work, Ernest Martin's muscle power test, and tests of more elaborate coordinated effort partly mental, partly physical. Economic tests of great importance have been widely used, especially the actual output of groups or of individuals or the amount of power used and other such. Or direct observations are made as to evidences of weariness and of symptoms, such as headache, sleepiness, lame feet, etc.; or the actual amount of sickness is determined or of time taken off; or there may be direct physical examinations of groups of people at periods to determine any change for good or ill in their condition. In England Captain Agnew studied thus 3752 men and boys, and a group of six women medical officers studied 1326 women and girls. There are various sources of error often quite unexpected to the uninitiated in any of these methods. One source of error which you will appreciate at once is that the better wages and consequent better living conditions than many had been accustomed to before in England have interfered a good deal with reaching accurate conclusions in some instances. They have, that is at times, led to improvement when otherwise one might in all reason have expected the contrary.

I would ask any clinician or physiologist how easy he finds it to determine clinically in a human being whether there is a slowly increasing general fatigue until the fatigue has become so marked as to be serious. But clinically in all sorts of work this is often extremely desirable to know and success in many a case goes suddenly to smash because we did not know how to determine this point. The English committee has done far more toward determining this in industrial work than has ever been done before and probably some of this work will become useful for general clinical purposes. In industry interest in this work is apparently beginning to penetrate quite widely. Many of you are aware that the methods of using the working forces of Great Britain as well as of France and Italy have been very considerably modified, as have the conditions surrounding them in their work, since the earlier days of the

war. An influence in leading to this that seems to have had a noteworthy part, directly or indirectly, in England, may apparently be found in these studies. In this country our committee has found the managers of factories in which the work has been done much interested in and impressed by the results and very ready to try out the suggestions that came from them. It is quite clear that it is very important to have the work sound and unbiased, if dependence is to be placed upon it in modifying things of such economic significance. I was recently asked by the executive secretary of the largest association of employers in the country to recommend to him a superior man and some younger men who should be preferably, note you, either physiologists or clinicians with a physiological training. He said that his organization wished itself to take up the study of industrial fatigue for practical purposes. Quite naturally it seemed to him that it was, in the first instance, a medical-physiological problem. I was, unfortunately, unable to help him to secure the men, partly because of war conditions partly because of the reluctance of scientifically trained men to touch anything that approaches the commercial. As bearing upon what I have just mentioned, let me remind you that at its recent meeting the American Federation of labor stated as an evident but extremely important fact that wages and hours of labor are the two great causes of conflict between capital and labor. It is scarcely necessary to insist that the most important thing in the world to-day, aside from this great war, is the conflict between capital and labor, and even in the war the social conflict has been almost as important as the military and may become the determining factor. Most of this conflict is due to the fact that heretofore these questions have usually been settled—as peace is usually made—in favor of the side that could exercise most force. It would be a vast benefit to the world if they could be settled by methods that would seem to both sides reasonable and sound and without bitterness. I think that it is in considerable part because they see possibilities of contributing largely to such a result that the gentlemen I mentioned have thought of engaging the services of physiologists or scientifically trained clinicians. It would be a grateful thing were medicine to play a noteworthy rôle in so large a drama.

I could add to the illustrations of the relations of medicine to industry, but to me it seems that those that I have very superficially discussed indicate that, somewhat quietly and only vaguely observed until they are upon us, there have grown up situations that are as yet undeveloped and still of uncertain significance and importance, but that do provide opportunities and responsibilities and require us to consider whether we have advanced as far in our point of view as medicine itself has potentially advanced, and whether, particularly, medical schools have done what they can do in future for the public welfare in this relation.

But before I go further with this query there is one more consideration that has perhaps an even more immediate interest to us and that I should therefore mention. In the discussion excited in this country by the proposed health insurance legislation it has been a general and wholly natural demand

of the profession that any broad legislation of that character must, if enacted, provide for the free choice of his physician by any insured individual. Sharing this desire and opposing this legislation, but still seeing well ahead, one of the sanest and ablest physicians in Massachusetts said to me that it is an impossible demand, or soon will be, that industry is so much more powerful than medicine that it will necessarily secure any just ends, whatever medical men wish, and that what industry needs for the sake of employer and employee alike is men trained to see and combat the hazards of industry, to get men well speedily in order to save time and disorganization and money to both sides, and to comprehend the economic relations of health in various ways as well as the psychology of groups of people.<sup>2</sup> I think that we need to consider whether the physician mentioned above did not speak truly when he said further that, in the increasing effectiveness of industrial organization, the whole vast body of industrial workers, and that means of course most people, might perhaps be gradually withdrawn from the clientele of individual doctors and hospitals and become the clientele of a medical service of industry—that that must happen or the profession must generally learn the needs of industry and practise them. That is a very radical thought when you consider its significance. It would take away the cake and leave only the icing. But we cannot dismiss it because it is radical. I personally think that the outcome will not be quite as he thought, but I nevertheless remember that five years ago, when I read Benjamin Moore's book picturing medicine as a national service built on a plan resembling that of the army, I thought skeptically that while perhaps coming sometime it was scarcely necessary for contemporaneous medicine even to think of adapting itself

<sup>2</sup> Let me make a little plainer what he meant by some of these points. One of the ablest industrial surgeons in the country told me that frequently he could not allow his injured men to go to the nearby excellent hospital because he could himself get them back at work safely and much more quickly by using measures that would seem distasteful to many fine conventional surgeons, but that are nevertheless practical. Of those he demonstrated to me, let me mention two little strips of tin fastened together in a form resembling a maltese cross which, when bent down on the four sides of an injured finger that has been dressed, and then covered with a bandage, permits a man to go back to work without discomfort or danger of infection very soon after even an amputation of a phalanx.

As an instance bearing upon economic relations and group psychology I would note that 18 months ago I became much interested in the number of cigar-makers with slight symptoms of cigar-makers' neuritis from one factory who were sent to us within a short time at the Massachusetts General Hospital by the Industrial Accident Board for an "impartial opinion" as to their suitability for compensation. I found that a man in this factory had developed a rather severe polyneuritis after an infection, and two doctors, taking his statement that the factory was exceedingly damp, without seeing the factory, had given the opinion that that was the cause of his neuritis and he had on this ground been given compensation. Many cigar-makers have, especially of course in the left arm, slight symptoms of neuritis, but so slight that they do not under ordinary circumstances especially notice them. This opinion, however, and the fear of severe results like those in the infectious polyneuritis case, had led to a consciousness of these

to that scheme. Nevertheless, a man who has greatly distinguished himself for wise administrative ability appears ready to propose legislation in England which in main principle is practically this same plan. And five years ago the whole British Medical Association was far more roused than ever before by the health insurance legislation, whereas now we see the official committee of that association reporting very favorably on its workings and recommending very striking extensions of it.

I do not wish to enter here a brief for any detailed future program to meet the situations that I have referred to. I wish simply, first of all, to ask myself whether, when I took up the study of industrial health as a collateral interest, I did not mistake for a hobby-horse a baby elephant that has since grown to some maturity and is now hard to guide or even to straddle and yet requires much skilled training to make him useful. I do feel impelled to ask again the question that I put a moment ago. In the very large strides that medicine has made in social and economic relations, have we physicians, individually or collectively, advanced fully with it? And since men are largely what their fathers made them, I may ask, Has the influence of medical schools upon students, that indefinable general atmosphere that is almost more influential than the facts taught—with all the increased keenness in the study of the nature, the diagnosis and the treatment of the individually diseased—has it imprinted upon them the unconscious habit of thinking of these broader relations with masses of men or has it still remained on the whole an individualistic atmosphere? I would not overlook the very patent fact that many men in the profession have lent this atmosphere conspicuously. I could scarcely do that in the

slight symptoms and an outbreak of excitement over the humidifying system. I visited the factory and it was a peculiarly sanitary one, but the walls being concrete one could observe a little condensed moisture upon them which in a wooden building would have been there in equal amounts, but would not have been visible. Nevertheless, the excitement led to forcing the owners into doing away with the humidifying system, probably to the disadvantage of both health and the work. I have had a number of experiences comparable with this one. On the other hand, some years ago Mr. Turner, then Commissioner of Labor, asked me to go with him and Professor Gunn to investigate the conditions and the men in the lasting department of a shoe factory where a new process had been introduced for making the box in the toes of shoes from celluloid, the latter being softened temporarily, in order that it might be fitted easily around the form, by immersing it in a mixture of acetone, denatured alcohol and a small amount of amyl acetate. The process had important technical advantages. The mixture made a disagreeable smelling stuff and the men complained of mild symptoms, such as disturbed appetite and slight headache, and some ardent leaders had brought on a strike in the whole factory, that threatened to have widespread significance, on the ground that their health was being gravely damaged. None of the men showed any actual physical damage, the exposure was mild and not likely to harm them, and they were assured that their symptoms were in no way serious and were due chiefly to the smell which could probably be mostly overcome by a blower system, which the owners agreed to put in. Chiefly as a consequence of this advice, I think, the strike promptly stopped.



place where Dr. Welch has reigned. I could not well do it and still recall the tablet on the wall of the medical clinic; and that same clinic now makes me share with you too keen and recent a sense of personal loss, a loss that involves, with all the rest that it removes, a rare development and exercise of the altruism that impels to public service and to the devoted application of precisely that sort of vision which I would wish that we all might acquire. There are individuals who do conspicuously lend this atmosphere. There are others here and elsewhere. With you I could name those who are "Somewhere in France." But I mean, Has this atmosphere become sufficiently general to hold its own in civil conditions against the daily study of the individual by the student of medicine and the young men who have graduated since medicine has assumed this character?

Just after writing the above—on a train—I met a layman prominent in this country in certain important community activities. By chance in a few moments, in another connection, he said to me that he has frequent dealings with both lawyers and doctors and that the chief contrast between the professions as they impress him in his work is that the doctor is usually an individualist, whereas the lawyer sees the community and, although the doctor is more frequently given to altruistic activities, the public-spirited lawyer usually accomplishes more because of his point of view. If that is really true, it is a matter of interest to us.

I am of course not thinking now simply of industrial health. Other great problems are with us and with them come great opportunities. For example, the Commissioner of Health of Massachusetts put me in the curious position of being chairman of the State Committee on Child Conservation, a committee born of the war, and as a member of the State Public Health Council I have for some time through another aberration of the same official been chairman of another sub-committee of that body, which among other matters has to give thought to the problem of the control of venereal diseases, the importance of which the war has so tremendously emphasized. The fact that I have occupied these two positions reminds me that Unna said once that the explanation of his having written so many books was that, whenever he was ignorant of a subject he thought he ought to know, he wrote a book on it. From this work I have learned at least that these two problems are, like that of industrial health, bewilderingly complex and vast in their importance; and I have likewise learned that while there are many pediatricians and obstetricians and syphilographers who are very skilful in diagnosis and treatment and in research, there are a few—but I think only a few—who have interest enough in these things as community problems to be of real assistance in guiding or coordinating general or local efforts to attack them. There are quite as many nurses if not more than there are practising doctors who, whether actually working in these things or not, know wisely and thoroughly the principles of etiology and of attack as community problems. Some nursing schools have for some time had elective courses for under-graduates in public health nursing and social service nursing, and there have been graduate courses in these subjects and in industrial nursing. In fact, opportunities for nursing work other than bedside nursing

exist now in such numbers and variety and are of such interesting character, that in schools where the atmosphere encourages attention to these things a surprisingly large number of nurses go into them. At the Massachusetts General Hospital Miss Parsons has been much interested in guiding nurses into these community activities. The effect is shown by the careers they take up at once. Of the nurses who graduated in the last three years the gross figures as to their present work, excluding the small number who are doing no nursing work, are as follows: Of the 1915 graduates nine are doing private nursing, 34 are in institutional, public health, social service, war work or other public work. Of the 1916 graduates 10 are in private work, 54 in public work. For the 1917 graduates the figures are 11 and 32. Institutional work naturally heads the list by far, but the other activities take a noteworthy share.

Have we been quite as forward-looking as the nurses? Medical opportunities of this sort are by no means all sufficiently reliable as yet to make it wise to lead many men actually into them as careers. But they exist and are increasing and a large reorganization and systematization of medicine is almost certainly coming in many ways, perhaps rapidly, more probably gradually, and this is likely both to excite a demand for many more men to work in special lines of such kinds, and also, what is more broadly significant to medical men, it is likely to make increasingly frequent opportunities for all medical men to mingle agreeably effectual strokes of prevention with their healing or their research. And it is likely that the doctor who cannot do this wisely upon opportunity will lose public confidence and prestige, for the public looks upon us already to a goodly extent as subsidiary health officers whether we feel it or not. Let me turn back to industrial conditions to illustrate this. Last summer I had a patient admitted to my wards with a diagnosis of purpura hemorrhagica. He was very interesting clinically in several ways, but he was almost unique in that he had had recurring attacks of hemorrhage for several years and had recovered from them while still continuing at his work, which the excellent fourth-year student who gave me the story told me at once was spreading the so-called "dope" in making artificial leather, a dope which contained, among other things that he mentioned, benzol. Although the patient had the usual blood conditions of essential purpura, the student correctly believed that the case was not one of essential purpura, but of benzol poisoning. Dr. Minot will report the case because of several important items in it. I mention it now because of the sequel. I wrote the manager of the factory, told him of the case and asked him if I might look at the process which I had never seen. I was welcomed by him, shown the details of the whole factory and told the composition of the dope, which the man had correctly stated. The exposure to benzol was very severe and the ventilation very bad. The manager called in the chemist and we went over the matter together, and as a consequence he told the chemist to get rid of the benzol completely if possible and said that he would look into a proper ventilating system. But he also told me that he had had a man die some months before with hemorrhages, and though he did not know that benzol was seriously poisonous he had wondered whether the



dope might not have had something to do with the man's death and had asked the doctors in the town who had had charge of the man if it had and they had said "No." He was a humane man and openly resented the fact that this advice had led him unknowingly to expose others unnecessarily. I could multiply similar illustrations. Let me mention one that illustrates well the common willingness of manufacturers to correct gross faults when pointed out to them and where means of control are indicated. In a very large plant engaged in producing raw material that is used to an enormous extent, as benzol is, in war as well as in peace, the company officers and the plant physicians have been much worried by the fact that there have been a considerable number of cases of an extraordinary and in some instances very grave disease in their men, and they did not know how to stop it. This disorder is most interesting clinically. It nearly always begins with a peculiar gait which one writer has aptly termed the "rooster gait." It advances to produce retropulsion and propulsion of a severity that is sometimes perfectly remarkable, and besides other manifestations it causes occasionally distinct mental changes. Direct physical examination shows almost nothing and there are not any focalizing signs. It seems to be chronic manganese poisoning. The company had gone to some expense to have a clinician well trained in the study of nervous disease carry out an investigation of the disorder. He made a clinical (and in a fatal case, pathological) study and did experiments on animals to attempt to determine the cause of the disorder. These observations were negative, but through finding in the literature descriptions of practically the same symptoms in a few instances in persons exposed to manganese, which is present in this plant in large amounts, he was able to determine the cause so far as anyone can now see. He made a valuable scientific report, but the company officials were annoyed because they said his report was simply an interesting medical paper and the thing that interested them was the economic and human matter of the prevention of the condition. The chief physician of the company was an old interne of mine and knowing that I was nearby he asked me to look over the situation with a view to further study of it. I took Dr. Cannon and Dr. Wade Wright along with me and we went first to see the plant. I only epitomized what they felt at once when I wrote that further study of the nature of the disorder would be interesting and profitable from a scientific standpoint and should be done, but that the imperative practical fact obvious to anyone that entered the plant was that the dust hazard was simply amazing and the dust contained at least one substance known to be poisonous and in all probability the actual cause of the condition, and the real thing to do was to have engineers devise means for reducing the dust—a difficult problem, but not more so than others that I had known to be solved. An executive officer of the company replied that they had had such plans under consideration for some time, but that he did not believe that they would prevent the disease. In view of my letter, however, he had ordered that they be taken up actively at once. The chief physician wrote me that he had been of my opinion for a good while, but had not been able to convince his superiors and thought that an outside opinion was necessary.

Very recently I have had letters from officers of the company saying that the large laboratory and technical equipment and staff of the company are available to carry out any plan of attack that I suggest. I have since had a conference with them and learned that they have nearly completed a system to control the dust at a cost of over \$300,000, and are now interested in having a careful study of the etiology and treatment of the disorder and they have given us at Harvard a generous budget for a two years' or longer scientific study of the whole question.

Things of this kind are about us in great numbers and of most varied kinds. No one can become an expert in such things without serious training, certainly not simply through exercising a hobby-horse. More experts are needed and I think that we should take steps to produce them. But the most effectual way of producing experts is not simply to provide opportunities for advanced training. There are now a goodly number of men who take up careers in the laboratory branches of medicine or in the application of these to clinical research. I can but believe that this is largely due to the fact that, with the present method of teaching medical undergraduates, all can now taste these careers in their student days and those attracted by them can thus early learn their attraction; while in former years they learned it only later, if at all, and then had often become too fixed in other work to make it easy to detach themselves from it. I imagine that it will in many instances be more through chance than through wise choice suited to the individual that men will go into these public or semi-public careers until that time when they become somewhat familiar with these aspects of medicine during their medical school days. Due regard for the public welfare makes it desirable to let the field be clearly seen so that those who are suited to special parts of it may enter them. But it is desirable not only for the production of experts; I am thinking less of advanced study than of the injection during undergraduate days of a sufficient modicum of knowledge to give a clear viewpoint to all. I might have drawn in this paper much more varied and interesting illustrations from the experience of experts than from my own observations, but I have purposely used my own almost exclusively because they constitute an example—but only one of course among the work of many others—of the fact that an unofficial clinician can scarcely avoid seeing and using frequent opportunities of this sort if he has been fortunate enough to have received early a stimulating injection such as Sir William Osler could administer. Unless medicine changes more violently and becomes more strictly specialized than I am now radical enough to believe that it soon will, there will be many opportunities for laboratory men and clinicians of almost all types to be influential in these things if they have acquired the point of view which, when practised and nursed for some time, leads to real usefulness even in the absence of systematic special training. After all, as in everything else, the strength of a health organization depends rather less upon the few experts than upon the fitness of the subordinates and of the rank and file through whom most of the details are done. We now recognize that teachers of physiology, chemistry, pathology, anatomy, pharmacology, medi-

cine, sing best not solo, but in chorus and following an "extended elaboration" of the theme. I have wondered whether we equally realize this in regard to the things that I have been speaking of and I have attempted to learn from some of my own students how much they feel these things in the general atmosphere in which they are growing up—not how much of a course they have had in them, but how much a part of real live medicine they seemed to them. I have not been made vain of my own accomplishments by what I elicited. Their feelings may only too often be briefly epitomized by the response of one man who naively remembered, "Oh yes we had *that part* of medicine finely in the course on preventive medicine—but that was in the second year." It was in "the old forgotten long ago." And yet there are those who think, and I am one of them, that medicine as a profession now deals so largely and with such increasing and fascinating effectiveness with problems of the mass, that there is a possibility and even some danger that before long not many of the best minds will be contented with the traditional ministrations to the individual. The latter will remain, I am sure, and should remain, the dominating duty of the great mass of the profession. But to feel that the other was through our inattention growing to be entirely out of our province would be a sad loss indeed to those of us not in official medicine. The coming generation in medicine will have opportunity to do much more of this grateful work than we; and do we not need to give them even more than our experience alone seems to indicate is necessary?

We need to keep clearly in mind, in our own activities and in teaching, the danger that the human appeal of the social problems with which we meet or the newness and fascination of the economic opportunities will distract us and our pupils from our legitimate fields of work. In the enthusiasm excited by new visions it is easy to overlook the boundaries of one's proper domain and to cultivate superficially and ineffectively distant territory that belongs to others while one's own is neglected. It is, I think, a wise recognition of this rather than simple inertia or lack of comprehension that has led many clinicians to hold off from these matters.

But we have now well reached that point in progress where we can see fairly clearly in these questions, where our contributions must be restricted to a sympathetic interest and attention and where, on the other hand, we have distinctively medical problems which offer a goodly yield of bettered health and can be attacked by accurate methods wholly agreeable to the scientific temperament and training.

Certainly in no field of medical activities, not even in infectious diseases, is there so frequently such precise knowledge of the principles of etiology and such accurate and dependable methods of study of etiology and prevention, and in none are there at present such manifold opportunities of contributing practically to improvement of health as there are in the field of industrial disease. And in no broad field are there fewer well-trained investigators.

As I view the situation in relation to the war, one of the serious needs at the moment is some organized body of highly trained men, including especially a physiologist, a chemist and an engineer, who should be seeking now for better understand-

ing and control of the existing hazards to industrial workers, and should be alert to recognize, investigate and prevent the dangers that will arise from increasing pressure and strain, especially perhaps from the restless inventiveness of this war. At present there is a real danger that adequate attention to these matters will be aroused at best only when serious damage has been done. Such a body could work effectively only if in cordial cooperation with the Federal Health Service and the Labor Department. Likewise seriously needed is a method of establishing officially minimal standards of prevention in hazardous industries and minimal medical examination and observation of employees in such industries. And with this there must be an official method of hygienic inspection of these industries to see that these matters are understood by the many manufacturers and employees to whom all this work is now very new, to determine that the regulations are followed, and when necessary to enforce their use. This work could most advantageously be done directly by the Federal Health Service with its already well-organized division of industrial hygiene acting in cooperation with the state authorities. This will come before many years throughout the states generally, but if the war is to continue long, it must be put in operation soon as a war measure if grave damage to health and industrial efficiency is to be avoided. If done later and gradually, it can be met gradually. If done soon as a more general measure, as should be the case, it will at once be evident that it must be badly done because of the lack of sufficient men trained in the medical inspection of industries and the equal lack of those trained as industrial physicians, unless there be undertaken a rapid intensive training of men for these duties just as men have been and are being trained intensively in a variety of forms of special military medical duties in which the demand is imperative and far greater than the supply. If this occasion arises it will give medical schools opportunity to repair somewhat the deficiency that would have been much less had we been more foresighted and will initiate them into what I think they will undertake before many years anyway. Moreover, it will give opportunity for part time or full time useful public service for some medical men who are for any reason unable to undertake military service.

Though there are many things to be said and though I have but hastily and superficially touched upon a few of them, I have perhaps seemed often to wander far from the war, as I warned you that I might do. Nevertheless, I have not been far from it in my thoughts. We have been violently taught by the war that through a continued system of education the Teuton has been made to think almost involuntarily and in innumerable ways of the State when carrying out actions that to us are simply those of common individual service. Many others than I have thought that if for the Teuton conception of the State, that of an idol to be worshipped and sacrificed to, we substitute the picture simply of those who make up the State, our educational methods may perhaps gain from the distorted example of our enemies the beneficent influence that they, and those from other lands who had been in contact with their education, had hoped they might have, but which they have so grievously failed to exert.

## A THYMUS TUMOR ASSOCIATED WITH ACUTE LYMPHATIC LEUKEMIA

By RALPH H. MAJOR

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The relationship between tumors of the thymus and leukemia remains a subject of much interest to both clinician and pathologist. Interest in this subject is perhaps heightened by the infrequency of such cases, since, as Schridde<sup>1</sup> has remarked, "With the exception of the bone-marrow the thymus is the organ in the body poorest in tumors." Because of this comparative rarity of thymus tumors and the association of some of them with leukemia, the following case, studied through the kindness of Dr. Watson Campbell, seems worthy of record:

The patient, M. P., a white woman, age 42, entered the Kansas City General Hospital on January 17, 1918, complaining of pains in the back. She stated that she had been weak and had had no appetite for a month. About two weeks before admission she had begun to have headaches and pains in the right thigh, radiating from the hip down to the right ankle. She had also found her vision in the right eye impaired and had complained that "everything looked crossed." Some cough and shortness of breath had been present.

Physical examination showed a rather obese woman with a somewhat pasty color. The eyes reacted to light, the left pupil was slightly larger than the right. There was a complete paralysis of the sixth nerve on the right side and partial paralysis on the left side. The teeth showed a marked pyorrhœa alveolaris, the tonsils were hypertrophied. The chest showed a few moist râles in the axilla, the spleen was enlarged and palpable. Reflexes normal. Blood-pressure 120/185.

The spinal fluid examined on February 1, 1918, showed a cell count of 20. Nonne negative; Wassermann negative.

A blood count on February 8, 1917, showed 3,400,000 red cells, 41,000 white cells, hemoglobin 60 per cent. A differential count showed polymorphonuclear neutrophils 12 per cent, small lymphocytes 35 per cent, large lymphocytes 30 per cent, transitionals 8 per cent, eosinophiles 2 per cent, myelocytes 4 per cent, degenerated forms 2 per cent, normoblasts 7 per cent.

The blood examination on February 11, 1918, showed 3,600,000 red cells, 21,000 white cells, hemoglobin 60 per cent. A differential count showed polymorphonuclear neutrophils 16 per cent, small lymphocytes 17 per cent, large lymphocytes 35 per cent, transitionals 9 per cent, eosinophiles 1 per cent, myelocytes 10 per cent, degenerated forms 1 per cent, normoblasts 10 per cent.

The patient died on February 12, the day following the second blood examination. The findings of the blood examination were clearly those of a lymphatic leukemia, and the short duration of the disease with the rapid course indicated the diagnosis of acute lymphatic leukemia.

The protocol of the autopsy, performed two and one-half hours after death, is as follows: The body is that of a white woman 165 cm. in length, weighing 65 kilos. The sternum is deformed, with an upward curve in the middle portion. Both lungs are crepitant and show some edema on cut section.

In the anterior mediastinum there is a rather firm, large tumor extending down over the heart (Fig. 1). This mass has a thin, tough, smooth capsule; on cut section it shows a dark reddish-brown color and is of a soft, spongy, slightly granular consistency. With the naked eye there are evident numerous connective-tissue strands running throughout the tumor dividing it into compartment-like areas (Fig. 2). When removed from the heart the posterior surface of the tumor is seen to be closely adherent to the parietal pericardium. The general shape and form suggest in appearance an enlarged uterus with its cervix turned upwards. The tumor measures 10 cm. in length, 7 cm. in width at the lower portion and 7 cm. in thickness; it weighs 189 grams.

The heart presents no especial abnormalities. The spleen is markedly enlarged, measuring 30 x 12 x 6 cm., and is very soft. The liver, pancreas, kidneys and uterus are all enlarged and of a soft, flabby consistency. The cervical, bronchial, mesenteric, retroperitoneal and inguinal lymph glands are all enlarged, but quite discrete. On cut section, all of these glands show small irregular areas of hemorrhage. The gross appearance of the brain is normal.

Microscopic examination of the liver, heart, pancreas, kidneys and uterus shows extensive infiltration with lymphocytes. In many sections this lymphocytic infiltration is so marked that the microscopic recognition of these organs is extremely difficult. Sections of the spleen show it to be filled with large and small lymphocytes and many myelocytes. Sections made from the brain show some infiltration with lymphocytes.

Paraffine sections of the mediastinal tumor were made and stained with hematoxylin and eosin, Van Gieson's stain and Mallory's aniline blue stain. Microscopic study of these sections (Fig. 3) shows that the tumor has a definite fibrous tissue capsule just under which in some places are areas of apparently normal thymus tissue. Most of the tumor is composed, however, of fine strands of connective tissue, in between which are masses of partly degenerated poorly staining cells, many of them lymphocytes and the others red blood cells. In a few places the cells are well preserved, and in such areas there are collections of small and large lymphocytes and some multinucleated giant cells. Also, there are here and there masses of cells different from the others and showing an epithelioid character. Areas of hemorrhage are very extensive throughout. There are also numerous large irregular masses staining



blue with hematoxylin and structures circular in shape, distinctly laminated and staining bluish or purple with hematoxylin. These structures resemble very much the so-called corpora amylacea or suggest degenerated Hassall's corpuscles. Degenerative changes are quite marked in all the sections.

The size of this mediastinal tumor, its shape and location, together with the microscopic picture, suggest strongly that we are dealing with an enlarged, persistent hyperplastic thymus which has subsequently undergone extensive degeneration with hemorrhage. The relationship between such a picture in the thymus and the clinical picture of an acute lymphatic leukemia is of interest in the light of the relationship between the thymus and the lymphatic system.

The possible rôle of the thymus as a leukocyte-forming organ was suggested by Ghika,<sup>2</sup> who concluded that the thymus is primarily a hemopoietic organ and forms leukocytes, but probably no erythrocytes. These conclusions of Ghika were not, however, supported by the later work of Noël Paton and Goodall.<sup>3</sup> These observers found that in guinea-pigs removal of the thymus produced a leukopenia which, however, was not persistent and passed away when the animals reached the age of sexual maturity. Schultz<sup>4</sup> found that in dogs removal of the thymus had no permanent effect upon the blood picture. As contrasted with these findings, however, Klose, Lampe and Liesegang<sup>5</sup> describe a progressive diminution in the lymphocytes in dogs which had been subjected to thymectomy. Klose describes further a lymphocytosis in dogs following injections of juice expressed from the thymus, and states also that in three patients upon whom a thymectomy was performed a permanent reduction in the number of lymphocytes followed.

The occurrence of an enlarged thymus in association with lymphatic leukemia has been noted by several observers. Obrastzow<sup>6</sup> observed a case of acute lymphatic leukemia in a boy of 17, associated with an enlarged thymus "the size of a fist." McCrae<sup>7</sup> in his study of lymphatic leukemia describes a case showing at autopsy an enlarged thymus gland measuring 13 x 4 cm. Sérard<sup>8</sup> has studied in detail lymphatic leukemia and its association with enlargement of the thymus. Her paper describes two cases, one in a girl of five and the other in a boy of 16. The thymus in the first case measured 8 x 6 cm. and weighed 150 grams; in the second case it weighed 60 grams. Rocaz<sup>9</sup> observed a case of acute lymphatic leukemia in a child of four, associated with a marked enlargement of the thymus which measured 12 x 10 x 4 cm. and weighed 200 grams. The cases of "pseudoleukemia" associated with an enlarged thymus such as those described by Eberth<sup>10</sup> and Fischer<sup>11</sup> are apparently cases of Hodgkin's disease.

Another group of observers have viewed this clinical picture from a different standpoint and regard the blood changes as secondary to the thymus condition. Palma<sup>12</sup> describes a case of primary sarcoma of the thymus with the blood picture of a lymphatic leukemia. In his case the thymus tumor was "as large as two fists" and there were metastases into the pericardium and pleura. Brigidi and Piccali<sup>13</sup> describe a malignant lymphoma of the thymus. Litten<sup>14</sup> describes a

round-celled sarcoma of the thymus and Coenen<sup>15</sup> reports a case of lymphosarcoma of the thymus, all showing the blood picture of a lymphatic leukemia.

These two groups of observers have in all probability described the same disease picture, since we seem to have no definite criteria by which to judge which is primary, the thymus tumor or the blood disease. Moreover, the relationship between lymphosarcoma and lymphatic leukemia is so close as to suggest that in some cases they are merely different manifestations of the same disease.

Sternberg in 1903 expressed the view that under the term "lymphatic leukemia" two disease processes were included. One group of cases showing increase of the small lymphocytes in the circulating blood with hypertrophy of the lymphatic apparatus and infiltration with lymphocytes in the various organs, he described as lymphatic leukemia. In the second group of cases he found an increase in the blood of the so-called large lymphocytes and at autopsy tumor growths in different organs. To this group Sternberg gave the name of leukosarcomatosis.

Sternberg's views have given rise to much discussion and he has defended them on numerous occasions. They have also been attacked notably by Graetz<sup>16</sup>, Herxheimer<sup>17</sup> and Fraenkel<sup>18</sup>, the last author maintaining that leukosarcomatosis has no connection with true tumor formation, but is simply a type of leukemia tending to form tumors giving an appearance of malignant growths. Herz,<sup>19</sup> after an exhaustive consideration of this subject, states that the majority of observers do not accept Sternberg's view that leukosarcomatosis is a special disease of the lymphatic apparatus, but look upon it as a leukemia of a sarcomatous character which falls into a lymphatic and myeloid type. In any case, Sternberg's work has been of great value in calling attention to the aggressive tumor-forming disposition of certain cases of leukemia, and his views have led to an emphasis upon lymphatic leukemia as primarily a disease of the lymphatic apparatus instead of a simple disorder of the blood.

It is of interest that in six of the cases reported recently by Sternberg<sup>20</sup> three of the patients had large tumors in the anterior mediastinum probably of thymic origin. It should also be noted, however, that tumors of the thymus have been described without an abnormal blood picture, as, for example, the case reported by Gamgee,<sup>21</sup> who described a lymphosarcoma of the thymus in a child of five who never showed any increase in the number of white blood cells.

Lochte<sup>22</sup> has studied an interesting condition of the thymus associated with acute lymphatic leukemia. In two cases he described a somewhat enlarged thymus in which an "epithelioid transformation" had taken place. Here the lymphoid elements of the thymus were not so striking, but there were numerous epithelioid cells, some of them multinucleated, lying free in a loose connective-tissue framework. He believed the thymus condition bore some relation to the blood disease and stated that such changes had not been observed in chronic leukemia or in pernicious anemia. Similar collections of epithelioid cells with multinucleated cells were, as previously

mentioned, noted in our sections, but they did not form a predominating picture.

The microscopic examination of the thymus in our case suggests very strongly that we are dealing with a persistent thymus which has undergone a marked hyperplasia followed later by an extensive degeneration. The marked deformity of the sternum, consisting of a bowing outward with a large deep depression on the under surface corresponding to the thymus, indicates that the enlarged thymus had been present before the onset of the acute lymphatic leukemia.

This patient with a persistent enlarged thymus developing an acute lymphatic leukemia recalls the views of Herz,<sup>22</sup> who lays stress upon the relationship between the status thymicolympathicus and lymphatic leukemia. In our case the suggestion is strong that the enlarged thymus was an indication of an abnormal lymphatic state predisposing to disease of the lymphatic apparatus which later manifested itself by the appearance of an acute lymphatic leukemia.

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#### DESCRIPTION OF ILLUSTRATIONS

FIG. 1. The enlarged thymus as it appeared lying on the heart. The thymus has been divided in two, only the left half showing in the illustration. The heart in the illustration was not that of the patient but a heart of the same size which was better adapted to photography.

FIG. 2. One-half of the thymus tumor. The tumor is nearly symmetrical.

FIG. 3. Photomicrograph of a section from the thymus tumor. (Zeiss obj. AA, oc. 4. Hematoxylin and eosin stain.)

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WIT AND SATIRE ON THE PHYSICIAN IN HEBREW LITERATURE<sup>1</sup>

By HARRY FRIEDENWALD, M. D., Baltimore, Md.

Satire made its appearance at an early date in Hebrew literature and has ever since enjoyed favor among the Jews. In the Bible there are numerous satirical passages. It is not surprising, therefore, that Hebrew writers should have used this form of literary expression to rebuke the physician or to condemn the medical quack.<sup>2</sup> It must be remembered that these have suffered in like manner in other literatures.<sup>3</sup>

The earliest satirical reference in Hebrew appears to be the statement in II Chronicles, XVI, 12 and 13:

And in the thirty and ninth year of his reign Asa was diseased in his feet; his disease was exceeding great; yet in his disease he sought not to the Lord, but to physicians. And Asa slept with his fathers, and died in the one and fortieth year of his reign.

This contempt for the physician did not prevail among the Jews, as is seen in the chapter on physicians in Ecclesiasticus, XXXVIII, 1, 15, in which the physician is regarded with honor as the agent of the Lord:

Honor the physician according to thy need of him with the honors due unto him; for verily the Lord hath created him; for from the most high cometh healing, etc.

The earliest Hebrew satirist during the Middle Ages who used his lash upon physicians was Joseph Zabara, who was himself a physician. He lived in Barcelona in Spain during the latter half of the 12th century. Zabara was a poet and wrote a work entitled "Sefer Shaashuim" (Book of Delight), containing proverbs, anecdotes and folk-tales, besides much material of a scientific character on the various branches of medicine and on other sciences. This work has very recently been re-edited by Davidson.

I have gleaned the following from Israel Abrahams' essay on "The Book of Delight":<sup>4</sup>

A philosopher, says Zabara, was sick unto death, and his doctor gave him up; yet the patient recovered. The convalescent was walking in the street when the doctor met him. "You come," said he, "from the other world." "Yes," rejoined the patient, "I come from there, and I saw there the awful retribution that falls on doctors; for they kill their patients. Yet, do not feel alarmed. You will not suffer. I told them on my oath that you are no doctor." . . .

<sup>1</sup> The writer gratefully acknowledges his indebtedness for help received from Professors L. Ginzberg, I. Friedlander, I. Davidson, of New York, from Dr. E. N. Rabinowitz, of Baltimore, and especially from Professor Alexander Marx, Librarian of the Jewish Theological Seminary of America.

<sup>2</sup> Quackery has flourished at all times. In the early part of the 9th century Rhazes wrote a severe condemnation of quackery, explained the methods of the quacks and the reasons why the populace is so easily won over by them. This interesting document has been translated from a Hebrew MS. and published by Steinschneider in Virchow's Arch., XXXVI, p. 570, and XXXVII, p. 560. Rhazes tells how he went to great pains to expose the knavish trickery and charlatany of the quacks, but he also shows the necessary limitations of scientific medicine.

<sup>3</sup> "The Evil Spoken of Physicians," Charles L. Dana, The Charaka Club, I, p. 77.

<sup>4</sup> Jewish Publication Society, Philadelphia, 1912, p. 12.

One rather longer story may be summarized thus:

Satan, disguised in human shape, met a fugitive husband, who had left his wicked wife. Satan told him that he was in similar case, and proposed a compact. Satan would enter into the bodies of men, and the other, pretending to be a skilful physician, would exorcise Satan. They would share the profits. Satan begins on the king, and the queen engages the confederate to cure the king within three days, for a large fee; but in case of failure the doctor is to die. Satan refuses to come out: his real plan is to get the doctor killed in this way. The doctor obtains a respite, and collects a large body of musicians, who make a tremendous din. Satan trembles. "What is that noise?" he asks. "Your wife is coming," says the doctor. Out sprang Satan and fled to the end of the earth.<sup>5</sup>

The next writer to whom I shall refer, one whose satires are renowned, is the poet, Judah Al Charisi, who lived in Spain in the early part of the 13th century. His home was probably Barcelona, which he describes as "the congregation of princes and nobles,"<sup>6</sup> and he travelled much, even to the Orient. He translated many important works into Hebrew.

Charisi's description of the itinerant quack has been excellently translated by Dr. Solomon Sohis Cohen and published in *The Medical Pickwick*.<sup>7</sup> The writer pictures vividly the methods of the quack who has collected great crowds about him. When they have left he calls him to account for playing the rogue's game and is answered thus:

"Truly I go about to seek a living,  
Even as God in His mercy may provide it for me.  
For the time is evil; hard as a rock have I found her,  
And in her heart there is no pity for my poverty.  
Therefore, when thou art minded unto chiding,  
Chide not me, but chide the time."

Another Hebrew poet of this period was Jedaiah Ben Abraham Bedersi, who was born in Beziers in 1270. He published his first poem when he was scarcely 15 years old, and at the age of 17 he produced his "Sefer ha-Pardes" (The Book of the Garden), an ethical work. He produced many other works, poetical and philosophical, as well as theological commentaries.

In the "Sefer ha-Pardes" we find the following medical maxims:<sup>8</sup>

1. Four things are sources of joy for four classes of men. The moon brings joy to thieves; sinfulness of the people to the king; immorality to enemies; and the wrath manifested by the Creator towards His creatures is a source of joy for physicians.

2. When you are in need of a physician, you esteem him a god; when he has brought you out of danger, you consider him a king;

<sup>5</sup> This story has been retold by two modern writers: by Robert Browning in his poem, "Doctor," and by Israel Zangwill under the title "Death and Marriage" in his book, "Without Prejudice," New York, 1896, p. 187. According to Professor Louis Ginzberg the story is "one of the many variations of an Indian fable." Comp. Benfey, "Pantschatantra," I, pp. 520-525, and II, p. 551.

<sup>6</sup> Graetz, III, p. 387.

<sup>7</sup> January, 1916.

<sup>8</sup> Published in Hebrew by J. L. Dukes, in the *Lebanon*, V, pp. 503-504 (Paris, 1868), from an Oxford MS.



when you have been cured, he becomes a human like yourself; when he sends his bill, you think him a devil.\*

3. The inhabitants of a city are under greater obligations to the physician than to the king.

4. There are two questions which are very puzzling: Who shall cure the city physician when he falls ill, and who shall execute the executioner when he is found guilty?

5. Two men may look upon the face of the king—the physician and the artist.

6. Two men are accompanied with much honor—the judge on leaving the court-house, and the physician on leaving the house of the sick.

7. There are many slight illnesses which the physicians declare serious in order to increase their fees.

8. Many physicians know nothing of medicine, but even the dangerously sick may be benefited by the expression of their faces and their well-spoken words.

9. When you select a physician, choose a friend and a man of experience.

10. Sudden death is a decree from heaven, for which the physician is not to be blamed.

11. Three classes of men, even when educated and cultured, are held in poor esteem: the foreigner, the libertine and the physician.

12. The thoughtless physician says, "What have you done?" The wise physician says, "Do thus."

13. He is no physician who has not slain many patients.

14. Two classes look forward to speedy wealth: the heirs of the sick in whom they rejoice, and pharmacists, who rejoice in physicians.

15. Most physicians you meet reach a ripe old age, because the Angel of Death wishes to give them a chance to increase his victims.

16. Were all physicians your friends rejoicing in your health, you would find no one to treat you (without pay) in your illness.

17. The physician and the musician will not be admitted after death either into the World of Reward or into that of Punishment. When the musician and the physician depart from this life, the former takes his musical instruments and his baton, and the latter his books and prescriptions and they approach the entrance of the gate of the World of Reward. There they request Methuselah and Noah to grant them admission. In reply to the question, "Who are you?" the physician says, "I cure all diseases and illnesses; I enable human beings to live a proper life and make their existence agreeable by guarding them against disease." The musician says, "I fill their hearts with gladness and turn the souls of men from sorrow to joy and I rescue them from an ocean of anxiety." Thereupon the gatekeepers declare: "You cannot enter here. We have plenty of joy; the light of divine inspiration shines down upon us; the company is highly respectable and sorrow and grief are so far removed from us that we have no need to be entertained by musical performances. Again, physical defects are unknown to us; we are in good health and need not fear any diseases. No illness can attack us that we should need a physician to cure it. But we would advise you to go to the World of Punishment which is full of bitter suffering. Perhaps you may be of some use to the poor unfortunates that dwell there in anguish." On hearing this, the physician carrying his books and the musician playing on his instruments, both shaking their heads, go in the direction indicated, until they arrive at the entrance to the gate of the World of Punishment. There they call upon Og

and Goliath the Philistine, the gatekeepers, to grant them admission. When questioned about their identity, they repeat their former replies and thereupon are told: "Leave this place at once. For music is of no avail in a place of wailing. The finger of God weighs heavily here and the dwellers cannot be helped by music and play, but only by their wailing. Nor can they be cured by any physician, for who can remove the disease which has been inflicted upon them except by adding new and terrible disease and suffering. Go to that high mountain that is headed towards the wilderness. When the musician falls ill, the physician shall cure him, and when the physician is full of grief, the musician shall gladden his heart with his music. Go thither; there you will find an acacia tree; its fruit shall serve as your nourishment and its leaves as your medicine. When your wives die we shall send them to you."

No less famous than those that I have cited was Kalonymus ben Kalonymus, a Provençal writer and philosopher (born in 1286, died after 1328). He studied medicine, but did not practice it. He spent some time in Rome on an important mission.

His writings and translations include a number of medical works. Among his numerous writings there is one entitled "Eben Bochan" (The Touchstone) an ethical treatise written in 1322. "The treatise is written in cadenced prose". . . . and reviews "all the social positions of which men are proud and proves their vanity." At the end he enumerates the sufferings of Israel during the three years during which he had written the book. In it he holds up the quack physician to ridicule. In a market-place, a man in gold-braided coat, with rings covering his fingers and with chains dangling over his waistcoat, is addressing the people that crowd about him. He tells them of his marvelous powers. Hirelings in the crowd whisper his praises. Many fools are induced to seek his help and pay him heavily.

Kalonymus explains the quack's method: Each case he regards with serious countenance; he discovers the ailment by looking at the urine; but the medicines required to bring about a cure are very expensive and he cannot prepare them without prepayment. The money is collected and then he proceeds to describe how to prepare his cure-all, with all manner of substances and ridiculous ingredients. If the patient recovers, it is well; if he dies, the quack in anger blames those who prepared the remedy for not carrying out his directions. Kalonymus condemns the quacks, because their art is lying and deception; all their boasting is empty falsehood; their hearts are turned away from God; their hands are covered with blood; wise teachers of the Talmud refer to them when they declare that certain "physicians are fit only for Gehenna."

While in Rome, Kalonymus won the friendship of another poet, Immanuel of Rome. Immanuel ben Solomon ben Jekuthiel, better known as Immanuel of Rome, a friend of Dante, was born in Rome about 1264 and died about 1330. He was a poet of distinction as well as a physician. In one of his stories an incident is related that occurred to the author in the course of his practice as a physician. He was called to a patient who suffered from indigestion, and who happened to belong to that class of people who fancy themselves endowed

\* This theme is repeated frequently by later authors, as we shall see below. The same theme is found in the *Regimen Sanitatis Salerni* (see translation by Ordronaux) and is reprinted in the *Annals of Medical History*, No. 1, p. 53, and ascribed to Cordus (1486-1535).

with great poetical talents. Immanuel prescribed some medicine for his patient and advised him at the same time to remain in bed till the following morning, when he hoped to find him completely recovered. But the patient . . . disregarded these orders, got out of bed and composed a long poem. This he showed with much pride on the following morning, telling his physician at the same time by way of reproach that the medicine prescribed was quite useless, and had produced no effect upon him. "Pardon me, my friend," said Immanuel, "my medicine has indeed had some effect upon you: it has removed from your brains a fair quantity of poetical rubbish."<sup>10</sup>

In another story Immanuel describes a physician's visit to a prude:

She lay on an elegant bed, putting the moon to shame with her beauty. . . . I approached to feel her pulse. . . . She covered her face and folding her garment about her arm, she said: "Feel my pulse through my dress." . . . I took a brick, placed it upon her right hand and holding a fire-pan in my own I felt her pulse with it and thus made sport of the lady. . . .

He next describes a mass of absurd remedies which he prescribed and shows that the young lady repaid doubly for her tricks.

The next satirist to be referred to is Galipapa, who wrote a Hebrew satire on physicians under the title, "The Physician's Aphorisms." A translation of this work has appeared in this BULLETIN.<sup>11</sup>

We shall now leap over several centuries and take up the satires of a modern Hebrew writer. The author to whom I refer is Isaac Erter, a physician who was born in Galicia in 1792, and died in 1851. He is well known as a brilliant Hebrew satirist. In one of his satires, "The Transmigration of the Soul," he tells of the adventures which a soul meets with, how it passes from one body to another, once leaving the body of an ass to enter that of a physician.

The soul informs the author that it had prospered greatly, not on account of its cleverness or ability, but because it had acted according to certain practical rules, and it recommends that the author follow them in his profession:

1. Powder your hair white, and place on the table of your study a human skull and some curious skeletons of the animal world. Those coming to you for medical advice will then say that your hair must surely have turned white through overwork in your profession, and through your protracted studies in the domain of natural science.

2. Fill your library with large-sized books that are richly bound in red and gold. No matter whether you ever open and read them or not, people will always have a high opinion of your great acquirements and wisdom.

3. Sell and pawn everything for the sake of having a carriage of your own. Your patients may die right and left through errors of judgment, yet the fact of having a carriage waiting outside their doors will shield you from adverse criticism.

4. If you are called to a patient you must pay less attention to him and his malady than to those persons who are around about

him. On leaving the sick-room assume a grave face, and say that the case is a critical one. Should the patient die, then you will have hinted at his death; but if, on the other hand, he gets well, his relations and friends will naturally attribute his recovery to your extraordinary skill.

5. Have as little as possible to do with the poor. For, as they will only send for you in hopeless and desperate cases, you will not gain any honor or reward by attending them. Therefore, be exceedingly reserved with them, and keep them at a distance. Let them wait outside your house, and those who pass by will look with amazement at the crowd patiently waiting to obtain your services.

6. Consider every medical practitioner as your natural enemy, and speak always of him with the utmost disparagement. If he happens to be young, then you must say that he has not had sufficient experience, and can do no good; and if he is old, you must declare that either his eyesight is bad, or that he is a bit demented, and is not fit to be trusted in important cases.

7. If asked to take part in a consultation with other physicians, you will be acting wisely if you always protest loudly against the previous treatment of the case by your colleagues. Whatever the issue of the case may be, you will be on the safe side.<sup>12</sup>

#### HUMOROUS AND SATIRICAL HEBREW POEMS

We find scattered through Hebrew literature many short poems bearing upon the physician. As a taunt at the too busy doctor take the following:

When Abraham Ibn Ezra, the poet (1088-1167), saw that it was impossible for him to earn a livelihood in his native country, he determined to try his fortune abroad. He thus visited Egypt at the time when the famous Maimonides (1135-1204) was the physician at the court of the Sultan Saladin. He made several vain attempts to see him and in the end composed an epigram of which the following is a translation:

I call on my lord in the morning,  
I am told that on horse-back he's sped;  
I call once again in the evening,  
And hear that his lordship's abed.  
But whether his highness is riding,  
Or whether my lord is asleep,  
I'm perfectly sure, disappointment  
Is the one single fruit I shall reap.<sup>13</sup>

The following selections are translations from Hebrew poems referring to physicians. The same themes are expressed in different poems, but for the sake of completeness they are all cited. Most of the poems are taken from a collection made by Steinschneider,<sup>14</sup> and reference to their source is indicated by "St." and the number given in his list at the end of each poem. No attempt has been made to render the Hebrew rhyme.

The following poem was written by Hillel ben Samuel, physician and philosopher in Italy in the 12th century, as an introduction to his translation of Bruno de Lungoburgo's "Chirurgia Magna":

Promise to serve everyone who is ill with thy wisdom  
But do not promise to cure a physician.  
Demand thy payment and the reward for thy service  
Whether he dies or is cured.

<sup>10</sup> From "Immanuel di Roma, a Thirteenth Century Hebrew Poet and Novelist," by J. Chotzner, *Jew. Quart. Rev.*, 1892, IV, p. 64.

<sup>11</sup> March, 1918.

<sup>12</sup> This translation is taken from Chotzner, "Hebrew Humour," London, 1905, p. 132.

<sup>13</sup> From Chotzner, "Hebrew Humour," p. 61.

<sup>14</sup> *Ztschr. f. hebräische Bibliog.*, VIII.

Eat not and sleep not at his home.  
 Let thy visits be only professional.  
 Then mayest thou ask him a double fee when he is cured.  
 Rely on a pledge and not on a verbal promise.  
 Serve princes in illness and accident.  
 Their gifts in showers will not fail you!  
 But if you attain to the service of the fair sex  
 Then you will be adorned with gold and jewels! (St. 16.)

The following poem is found in the Zabara collection and is also quoted by Shem Tob Ben Joseph Palquera, a poet of the 13th century and perhaps a physician, who recommends the practice of medicine as the noblest of all professions. It has been put into English rhyme by Ettleson:<sup>1</sup>

Quoth Fate unto the Fool: A doctor be,  
 Who, killing folks off, netteth income large;  
 So hast thou vantage o'er Death's Angel;  
 He must take the lives of people free of charge. (St. 5.)

The following is a parody on the preceding and was written by Solomon de Perea, a Spanish poet, about 1400:

Said Time to the shrewd one: A doctor be  
 And cunningly array thee in crimson  
 Thus art thou preferred to all men of wisdom  
 Who are clad in black because of their knowledge. (St. 4.)<sup>2</sup>

The two following poems were written by Isaac ben Solomon Al-Habib, who lived about 1370-1426 in Sicily, and who was the author of astronomical works:

Old men asked the Doctors  
 To straighten the rounded back of the aged.  
 The physicians answered that time had made crooked the  
 back of the old man  
 And who could make it straight? (St. 9.)

A full wallet cures the sick  
 Fattens the lean, gives strength to the weak  
 But its lack is a sore ill  
 For which the Doctor's wisdom is of no avail. (St. 12.)

The following was written in Spain in the 14th-15th century:

For each person will clothe himself in sickness as in a  
 garment.  
 Approach and see the answer.  
 In this book will be revealed immediately  
 The cure and relief.  
 Truly if medical books were lost  
 This one alone would teach thee how to cure. (St. 15.)

The following is found in a number of Spanish and Italian manuscripts of the 14th and 15th centuries:

When the ailment increases the doctor is exalted;  
 Then is he called prince and leader.  
 Lip vows and offerings are showered upon him  
 Nor is there a dearth of kind words.  
 He promises a house filled with good things,  
 A possession of field, yea, and a fortified town.  
 But as his health returns he rejoices;  
 When his ailment begins to depart  
 He recites the Hallel (a prayer of praise)  
 The Ahabti (Ps. cxvi) and the Min Ha-Mezar (Ps. cxvii. 5).

When he again begins to take food,  
 To drink wine and to eat meat  
 Then he says "I shall not see the Doctor."  
 When he demands pay for his service, as is right, he says:  
 "Behold in him Satan asking for reward:—  
 "When I see him my strength leaves me.  
 "Verily it is God who heals without charge,  
 "He gives bread to all flesh,  
 "He heals the sick, but not the physician.  
 "Through an angel he cures the distressed."  
 He asserts that the Creator has removed his affliction.  
 "He who does good to all his creatures."  
 He says that words of promise  
 Do not hold when uttered under pressure.  
 "If I made a vow, it is no vow.  
 "If I bound myself, there shall be no binding.  
 "My vows are absolved  
 "As to drinking and to eating." (St. 6.)<sup>3</sup>

This theme is similar to that cited by Ordronaux, "Code of Health of the School of Salerno" under "How to Forestall the Ingratitude of Patients."

The following was written about 1400:

Do not think that you can evolve the book of medicine out  
 of your understanding.  
 You must receive information from those who have pre-  
 ceded you  
 So that through them you will reach perfection. (St. 3.)

This poem is found in a Spanish, an Italian and an African manuscript of the early part of the 15th century:

The fool despises the physician,  
 And does not look to him for help.  
 He ascribes to nature  
 All cures and healing.  
 He denies the evidence  
 The Lord placed in this Law:  
 "For the Doctor he shall pay." (St. 13.)

The two following poems are found in three Spanish manuscripts of the 15th century:

The countenance of the doctor is like that of angels, exalted;  
 In the eyes of the patient while the pains are increasing,  
 His words are sweeter than dripping honey,  
 And are listened to as the voice of the Lord from among the  
 Cherubim.  
 But in a little while when his pains abate,  
 Lo, he is looked upon as other friends.  
 And when health returns  
 And the Doctor asks for his gold pieces  
 He becomes like unto Satan in the form of a man  
 And his words are not sweet to the ears. (St. 18.)

Oh Doctor!  
 At night shed thy light like the moon  
 (In our trouble do thou afford relief)  
 And promptly do thou bring redemption  
 To the heart that is aching and the entrails in pain.  
 He that places his trust in thee  
 That "captive exile shall speedily be loosed." (Is. li, 14.)<sup>4</sup>

<sup>1</sup> A vow made under compulsion is no vow. Cf. Nedarim 3, 4 and Gemara *ad loc.*

<sup>2</sup> Rashi's commentary on Exod. xxi, 19.

<sup>3</sup> (The biblical verse continues "and he shall not die and go down into the pit.")

Prepare thou for him a remedy against his destruction. (St. 19.)

<sup>4</sup> See Jewish Quart. Rev., N. S., I, p. 159.

<sup>5</sup> I. e., Charlatanry brings greater advantage than the real wisdom of the scholar.



The three poems which follow are taken from the appendix to Judah ben Shabbethai Ha-Levi's "Milhemet ha-Hokmah weha-Osher" (end of 12th century) which was published in Constantinople in 1543. It comprises 31 short poems, of which the following are 1, 13 and 27:

Every ill man fears death and hopes that he may be cured;  
And when told that the physician is coming, he feels happy  
And he longs and waits for the utterances of his mouth.  
For this reason any fool and inexperienced man finds it  
possible to be a physician.

\* \* \*

A learned physician,—how lovely! But the most honored  
is he

Who practices, whose own eyes see the diseases, and who  
Makes money when he raises himself [when he is proud?].  
Therefore, learn to get practice and stretch forth your  
Hand to take either ox or sheep, for the main thing is not  
To learn, but rather to practice.

\* \* \*

Mighty in song and higher in rank than a captain of fifty  
Is the glory of the medical profession, having a name  
among

The thirty [heroes of David]. On the day of Purim, send  
(the doctor)

A double gift to bring joy to God and man.

The two following poems appeared in a collection of short  
poems published in Constantinople in 1577; they are reprinted  
in Davidson's edition of Zabara, p. cxxii.

I am astonished at the physicians of our time,  
When I behold their deeds and their deceit!  
I saw them assembled near one (who called)  
For their help and for relief from his ills;  
When they cure they boast of the glory of their work,  
But when they take life they say that God has killed;  
They lay blame upon the sick who are innocent,  
Yea, in vain "they made long their furrows" (Ps.  
cxxxix.)<sup>20</sup>

They demand great pay for shedding blood and  
Fill their money bags with silver!<sup>21</sup>  
Is there anything like their evil in the world?  
Can the earth endure their insolent arrogance?

\* \* \*

He, who wishes to be a doctor  
Yet is a fool and an ignoramus  
Better that he be a baker  
And his name be not known. (St. 26.)<sup>22</sup>

The following was found by Professor Marx in a manu-  
script<sup>23</sup> among a number of satirical epitaphs, composed by  
Immanuel Frances (born in Mantua, 1630, died in Leghorn,  
1703):

Give thanks, oh reader, to the Lord, your Creator,  
That you never fell into the hands of this doctor.  
For you would not now read this poem  
If while he lived, he had been your doctor.

The following is a preface to the work on "Diet" by the  
renowned R. Isaac Israeli; it was placed in the Hebrew edition  
by some translator:

Clothe thyself in Doctor's garments and don fine raiment  
When visiting princes and the sick;  
Examine well the body of the patient and his symptoms;  
Judge according to all the affected limbs;  
Do not open thy mouth and lips in vow  
Until he weighs out for thee his silver shekels!  
And if the signs appear well in thine eyes  
Serve him as a Prince and Ruler.

Keep up thy courage, do not be confused  
And do not promise to raise high the low [i. e., cure the  
sick],

And do not assure a cure or relief.

For know that it is not in thine hand to accomplish it,  
But to God alone is the power  
And to the physician it is possible with this help to bring  
recovery.

The man who is sick is like unto a ship  
In the midst of the sea, and the physician is the pilot.  
With the lips of thy mouth speak pleasing words,  
Let thy face shine upon the Jew and Gentile  
And with the hand of righteousness  
 mete out kindness,  
With tongue of kindness utter words of wisdom.  
And guide them in eating and drinking, following  
This book of dietetics.  
Study it and look carefully into the book  
Which was composed by R. Isaac, the man of great  
deeds. (St. 14.)

The three following poems were published by Moses Hayyim  
Soschino in 1778:

How is it—I wondered—that the man I know for a fool,  
the people regard as a physician  
And empty into his hand their bags of wealth?  
But perhaps this reward is all his profit,  
For well have (the Rabbis) said,  
"The best of physicians is doomed to Gehenna." (St. 2.)<sup>24</sup>

\* \* \*

A famous physician has taken up his abode  
In the assembly of the dead.  
He intends to cure them and bring them to life,—  
Therefore has he set up his throne there.  
But behold like the messengers of Saul  
He will remain with them  
Until the days of transgression and sin are over.  
Till then, master, you will not be ransomed! (St. 20.)<sup>25</sup>

\* \* \*

All ye inhabitants of the earth sing with glee!  
See, the dead are to return to life  
For a doctor has gone to them to cure them  
See, the exile of Edom and Yavan is at an end;  
ended is the exile of Babylonia. (St. 10.)

The four poems which follow are without definitely assign-  
able dates but were probably composed in the 15th century:

Ask, oh Doctor, ask thy reward from those that seek thee  
And accept it on the day that thy service pleases,  
Remember that the sick forget on recovering  
All your drugs and medical remedies. (St. 21.)

\* \* \*

<sup>20</sup> Prolong their explanations for their failures.

<sup>21</sup> Play on word "Damim," i. e., money and blood.

<sup>22</sup> Play on the words "Rophe" (physician) and "Ophe" (baker).

<sup>23</sup> The manuscript is "Halberstam 437," fol. 74d, now in the  
Library of the Jewish Theological Seminary, New York.

<sup>24</sup> Talmud, Kiddushin iv, 14.  
<sup>25</sup> According to Steinschneider this is a humorous epitaph.

I met a physician and asked him why  
Are your garment and your head red?  
Are your garments as one who treads in a winepress  
(Is. lxiii, 2),  
Or is it the blood of those you have slain? (St. 25.)

Where is the physician who understands the body,  
Who distinguishes like from unlike,  
Who recognizes which humors ascend and which descend,  
Which will grow weak and which will grow strong,  
And what can cause them to be changed;  
What will "break the snare"<sup>26</sup> [cure the disease]?  
I sought him but I did not find him.  
There is none to choose the grain from the chaff!  
I found the physician lying in wait<sup>27</sup> with his cane,  
With no care whether the live be buried.  
I ask him how he can thus shed blood.  
He answered "This is the way of men." (St. 1.)

The honor of the physician and the time of his highest  
esteem are in the spring  
In all [the months of] Sivan, and of Tammuz and of Ab.

<sup>26</sup> Ps. cxliv, 7.

<sup>27</sup> Exod. xxi, 13.

Man!—know and understand; see that in these months  
The Lord causes his creatures to be sick.  
Remember, the physician is like unto the Hebrew bride-  
groom who invited his guests;—  
When they come, he is respected as a prince,  
When they leave, he is treated like an orphan.

The poems here cited are for the most part found in a number of different manuscripts. Professor Alexander Marx, who directed my attention to them, concludes that they must have enjoyed wide popularity.

The selections which I have given show that the physician was often made the target of wit and satire in Hebrew literature—but only the ignorant, the unscrupulous, the pretentious and the quack. No people has more consistently shown its regard for the profession of medicine than have the Jews. They have devoted themselves to medicine as a favored profession in all the ages of their history. They have laid down rules of ethical medical conduct that have never been excelled. Their scorn for the quack and the charlatan was as intense as was their admiration and respect for the "faithful physician"—a term which, in greatest reverence, they applied to God.

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# BULLETIN

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## MYRTOL POISONING; WITH COMMENTS UPON THE TOXICITY OF EUCALYPTUS OIL AND MYRTOL IN HUMAN BEINGS AND IN ANIMALS

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On account of the toxic symptoms that sometimes follow the administration of oil of eucalyptus and allied substances, it would seem worth while to report the following case of alleged poisoning by myrtol:

### CLINICAL HISTORY

The patient, a gentleman 42 years of age, consulted one of us on January 10, 1911, complaining of cough with a large amount of offensive sputum. The family history is negative for tuberculosis. The patient had pneumonia at the age of 21, since when he has had more or less cough and sputum. During the past five years the cough has been worse and a considerable amount of sputum has been coughed up each morning. Five years ago, after an acute cold with sore throat, he suffered from hæmoptysis, coughing up half a teacupful of blood. Repeated examinations for tubercle bacilli were made, but none was found. There was no fever during the attack. In September, 1911, before consulting us, he had had an acute bronchitis accompanied by slight hæmoptysis. This was followed by a bronchopneumonia involving the upper lobe of the right lung, the illness lasting over one month. Many examinations for tubercle bacilli were made during this period,

always with negative results. An autogenous vaccine was prepared by his local physician against some microorganism grown from the sputum and five doses were administered.

*Note made on January 10, 1911 (Dr. Barker).—*The patient now feels very well, though he still coughs up a considerable amount of sputum, especially in the morning, and this sputum is very offensive at times. The total amount raised now is about four ounces in the 24 hours. There is no pain and no dyspnoea. The voice is occasionally hoarse. No night sweats. No marked digestive disturbance. Weight 227 pounds. Height 6 feet 2 inches. The weight was 245 pounds before the attack of bronchopneumonia.

*Physical Examination.*—Slight protrusio bulborum; positive von Graefe's sign. Defective teeth. No struma. No glandular enlargements.

Right upper chest flatter than left in front. Right mammilla on lower level than left. Expansion greater in left chest; right lung lags behind. Breath sounds slightly prolonged at right apex, and the percussion note is a little higher pitched there than on the left. No râles audible in upper lobes. Fremitus somewhat more marked over the right suprascapular region than over the left. Breath sounds distant at the right base. A distinct creaking sound is audible at the right base, and some distant moist râles can be heard there. Breath sounds and voice sounds are distant over right lower lobe behind.

Heart negative. Abdomen negative. Reflexes normal.



*X-ray Examination* (Dr. F. H. Baetjer).—Stereoscopic and radiographic examination of the chest shows increase of fibrous tissue around the bronchi and the bronchial ramifications in both lungs. Some enlarged glands at the hilum of the left lung. Left lung substance clear throughout.

A peculiar shadow is seen at the base of the right lung, obliterating the diaphragm and the base of the right lower lobe. This shadow is probably due to a thickened pleura and to some fibroid change in the lung itself. In the upper part of the right lower lobe the bronchial tree can be distinctly made out. There is a suggestion of a bronchiectatic cavity in the right lower lobe, but there is so much fibrous peribronchial change that no definite statement regarding it dare be made.

*Diagnosis*.—Bronchiectasis; bronchitis chronica putrida; peribronchitis fibrosa; pleuritis chronica dextra.

*Treatment*.—In addition to general measures, three minims of myrtol in capsules thrice daily were prescribed on account of the foetid bronchitis. The patient had been taking some oil of eucalyptus and oil of sandalwood before. These he continued along with the myrtol.

*Further Course*.—January 16. The patient reports that the myrtol is already lessening the putrid odor of the sputum.

February 13. The patient writes from the Pacific Coast that he has suffered strange and severe symptoms since taking the myrtol prescribed. After having taken two capsules three times a day for eight days "the face became discolored and large 'puffs' came under each eye. The forehead looked as if it were going to break out with eczema. The left eye became nearly closed and the right partially closed from the swelling."

Fearing an attack of erysipelas he called a local physician, who, with the nurse, agreed that the symptoms must be due to the poisonous effects of the myrtol. The drug was stopped at once, but the swelling lasted for many days. The patient states that the cough increased markedly and that the heart's action became more rapid, and that he was greatly depressed. He had been told to increase the dose of myrtol gradually until 12 capsules per day were taken, but the myrtol was stopped when only six capsules per day were ingested. He states that the discoloration of the skin and eruption covered the entire chest also.

February 23. The patient writes that he and the nurse feel entirely convinced that the whole trouble was caused by the myrtol. He sends the bottle containing the unused portion of the drug that experiments may be undertaken with it. It was purchased from a druggist in Baltimore, who stated that it had come direct from Merck's in New York.

In one of the patient's later letters, he states that he is not sure that the offensive odor of the breath was really decreased by the myrtol. He also states that while on the train going toward the Pacific Coast, during the last two days of the trip, he was in serious doubt as to whether he would reach his destination alive.

Here we have evidently to deal with an instance of myrtol intoxication, probably exaggerated by the oil of eucalyptus which was taken at the same time. The striking phenomena observed in this patient, never before observed by us notwithstanding a considerable earlier experience in myrtol administration, led us to try some experiments on animals and to review the literature of the subject.

#### SOURCES OF MYRTOL AND EUCALYPTOL

Myrtol, obtained by distillation from the leaves of *Myrtus communis*, is a mixture of a dextrorotary terpene (known as cineol), pinene,  $C_{10}H_{18}O$  and dipentene. The myrtol, on distillation, comes over between  $160^{\circ}$  and  $180^{\circ}$  C.

Oil of eucalyptus is a volatile oil distilled from the fresh leaves of eucalyptus, rectified by steam distillation; it yields, when assayed, 50 per cent of eucalyptol.

Eucalyptol ( $C_{10}H_{18}O$ ) is the chief constituent of the eucalyptus oil obtained from *Eucalyptus globulus* and some other species. It is an organic oxide (optically inactive) isomeric with cajeputol (levorotary), and with cineol (dextrorotary). In the distillation of eucalyptus leaves the portion that comes over between  $170^{\circ}$  and  $178^{\circ}$  C. is set aside as crude eucalyptol. When redistilled from potassium hydroxide, pure eucalyptol is obtained.

The large natural order, *Myrtaceæ*, includes many genera. Among them besides *Eucalyptus* and *Myrtus* may be mentioned *Pimenta* (allspice) and *Eugenia* (cloves). The oils from these several myrtaceous species are utilized to a considerable extent as remedial agents.

Eucalyptus oil, eucalyptol, and myrtol find their chief value in therapeutics, at present, in the treatment of catarrhal conditions of the respiratory mucous membrane; they are administered either internally (on sugar, or in capsule) or with steam in the vapor from an inhaling apparatus. They are also occasionally employed (1) in chronic inflammation of the genitourinary mucous membranes; (2) locally as an antiseptic dressing to ulcers; and (3) also as counterirritants in neuralgia and rheumatism. Eucalyptus oil and eucalyptol are usually administered in 5-10 minim doses and myrtol in 5-15 minim doses, in capsule, four to eight times a day.

Formerly, eucalyptus oil was utilized much more extensively than at present. It was thought to possess considerable value as an antiperiodic and hence was widely used in the treatment of malaria. It was administered in these cases in large doses (usually from  $\frac{1}{2}$  to 1 drachm) two or three hours before the expected paroxysm. The subcutaneous administration was frequently resorted to, the oil being diluted in olive oil (1 in 4 or 1 in 10). It has also been used locally in the treatment of various skin diseases, *e. g.*, in eczema, prurigo, psoriasis, impetigo and condylomata. Recently, since Dakin's introduction of chloramin therapy, oil of eucalyptus has begun to be extensively used, and it will be interesting to observe whether many instances of intoxication are met with.

#### ANIMAL EXPERIMENTS (DR. ROWNTREE)

Some experiments were made upon dogs and cats with myrtol and with eucalyptus oil in order to determine their toxicity. The data relating to the myrtol experiments are first presented. Since the bottle of myrtol used by the patient was only partially emptied, the remainder was available for study. It is here designated as Preparation I. Another sample of myrtol (Preparation II) was obtained from a local druggist. The drug was administered to the animals through a stomach tube.

TABLE I.—EFFECT OF MYRTOL ON DOGS

Dog	Weight in kg.	Date	Amount administered	Condition of animal
I	9.9	3-11-11	1 c. c. of Prep. I.	No abnormality noted.
		3-13-11	5 c. c. of Prep. I.	Dog did not vomit this. He took his food and drink normally. He remained normal.
II	9.3	3-11-11	0.8 c. c. of Prep. I.	This dog remained perfectly normal throughout the period of observation from March 11 to March 25.
		3-12-11	2 c. c. of Prep. I.	
		3-14-11	2 c. c. of Prep. I.	
		3-15-11	2 c. c. of Prep. II.	
III	6.2	3-13-11	2 c. c. of Prep. I.	Vomited five minutes after first administration. Remained free from vomiting after other doses until the 22d. On this date the dog vomited 10 minutes after the administration. The vomited oil was intimately mixed with meat. The dog ate this again and was entirely normal after it. No sign of a skin lesion developed.
		3-14-11	0.5 c. c. of Prep. I.	
		3-16-11	2 c. c. of Prep. II.	
		3-17-11	2 c. c. of Prep. II.	
		3-18-11	2 c. c. of Prep. II.	
		3-19-11	2 c. c. of Prep. II.	
		3-20-11	2 c. c. of Prep. II.	
		3-21-11	2 c. c. of Prep. II.	
		3-22-11	2 c. c. of Prep. II.	
IV	5	3-15-11	0.5 c. c. of Prep. I.	This dog remained absolutely normal until the 21st. On this date coryza and diarrhea were noted. Dog developed a typical distemper and so was discarded. No skin rash.
		3-16-11	0.5 c. c. of Prep. I.	
		3-17-11	0.5 c. c. of Prep. I.	
		3-18-11	0.5 c. c. of Prep. I.	
		3-20-11	0.5 c. c. of Prep. I.	
V	5	4-5-11	5 c. c. of Prep. I.	Dog did not vomit. No ill effect noted.
VI	4	4-2-11	2 c. c. of Prep. II every day for a period of two weeks.	Outside of a slight loss of appetite no abnormal condition was noted. No rash appeared.

Careful examination of the skin was repeatedly made on all of these animals, but at no time was there noted any skin rash ascribable to the drug.

In the following experiments, however, severe toxic phenomena followed subcutaneous and intraperitoneal administration.

*Exp. VII.*—Dog. 7.3 kg. Very playful. Pulse 150, respirations 36, temperature 38°.

12.24 10 c. c. eucalyptus oil in 30 c. c. olive oil subcutaneously.

12.30 Has lost playfulness, will not eat meat. Marked odor to breath. Sits in the corner, saliva dripping from mouth. Pulse and respiration unchanged at 12.40. Dizzy, does not respond well to prodding, apparently somewhat anesthetic.

1.20 Pulse 180, respiration 36; very dizzy.

3.20 Staggering, lies in a corner. Faeces and urine passed and the dog lies in them. Pulse 180. Pupils normal.

5 p. m. Respiration 30, temperature 39°. Marked collapse. Pulse cannot be felt, but a rate of 200 is determined by auscultating heart. Dog has been lying in her urine and faeces; can scarcely walk. Pupils slightly larger than normal, and contract to light.

7 p. m. Condition unchanged.

The following morning the animal had the odor of eucalyptus on its breath, but was running about, apparently in

normal condition. Pulse 104, respiration 24, temperature 37.5° C.

Two days later: odor still present in breath. Faeces and urine free from odor. Dog normal.

*Exp. VIII.*—A cat (1.8 kg.) was given subcutaneously 5 c. c. of Preparation II in 15 c. c. olive oil on December 8. After 10 minutes it seemed somewhat restless, but otherwise normal. The pulse, respirations and temperature remained unchanged during a period of observation of five hours. On December 9 the animal was somewhat ataxic, presenting a staggering gait. It refused to eat or drink. The breath smelled strongly of eucalyptus oil. The pupils remained normal. The urine was dark in color, showed a trace of albumin, but no sugar. Casts and blood were absent. Respiration, pulse and temperature normal. On the following day the animal was much better, walked without staggering, but still refused water and food. Urine showed a slight trace of albumin. On the 11th it drank milk and took its food and was apparently normal again.

*Exp. IX.*—Eucalyptus oil in toxic doses was also administered to two cats. Cat I (2 kg.) was given 10 c. c. of eucalyptus oil in 30 c. c. of olive oil intraperitoneally at 12.30. At 12.38 it appeared unsteady on its feet and swayed from side to side when attempting to walk. Stringy mucus was secreted from the mouth. At 12.40 it huddled up in a corner and refused to move. At 12.47 all power of motion was lost. The animal apparently was anesthetized inasmuch as no response to prodding with a needle could be elicited. A slight clonic convulsion was seen at 12.50. This became more marked, following any sudden sharp noise, *e. g.*, clapping of hands. Respiration normal, pulse 112. Temperature 37° (normal, taken before giving oil, 38.5° C.). The pupils remained normal. Animal comatose. Death at 2.30 p. m.

*Exp. X.*—Cat II. (1.8 kg.) 10 c. c. eucalyptus oil at 1 p. m., subcutaneously. The animal appeared dizzy at 3 p. m., staggering on attempting to walk. At 8 p. m. this was more marked. The following morning the animal was found in a semi-comatose condition. Convulsions occurred at intervals. Temperature was low, 29° C., by rectum. Pulse 92, respirations 14. Urine high-colored and scanty, containing blood and albumin, but no casts. The odor of eucalyptus on breath was very marked. Chlorobutanol gm. 1.0 was administered, followed by death in the course of an hour.

Bruning has determined the toxicity of eucalyptus oil for animals and finds that, in the frog, 0.5 c. c. per kilo caused only temporary paralysis, in toads 1 c. c. per kilo did not kill constantly, in fish a solution of 1:10000 was tolerated, in chickens 0.3 c. c., in rabbits 1 to 5 c. c. and in guinea-pigs 1 c. c. per kilo was not fatal. He states that small doses are dangerous to children and advises against its employment in the treatment of ascaris lumbricoides.

## REVIEW OF LITERATURE

In looking over the literature nothing seems to be recorded regarding the toxicity of myrtol, but with eucalyptus oil we find that cases of poisoning have not been uncommon. The cases reported may be divided into two classes:

I. Cases in which overdoses have been taken accidentally or through ignorance, following which grave symptoms of intoxication have been present; some of the patients recovered more or less gradually; some died.

II. Cases in which the patient has responded in an unexpected and unaccountable way to minute or therapeutic amounts of eucalyptus preparations.

CASE I.—Beginning with cases of the first class: Wood (1879) reported a case of poisoning with belladonna and eucalyptus. A man, aged 48, received ½ ounce of belladonna root together with

3 drachms of eucalyptus oil. Six hours later, when first seen, he was unconscious, with widely dilated pupils which did not respond to light. Pulse 110, full and strong; respirations rapid. Spasmodic twitchings of the extremities. After the stomach had been emptied with a tube, the patient was stimulated electrically and on partial revival was made to move about and to walk between assistants for a period of five hours. At the end of this time he was still in a dazed condition and was hyperæsthetic over the whole skin. Strong coffee and milk were given and also 4 minims of tincture of opium. On the following day, dryness of the throat, thirst, and pruritus were complained of. At the same time, the skin of the patient showed a red blush, which lasted for two days. At the end of two weeks, the patient left the hospital, apparently in a normal condition.

CASE II.—Owen (1885) made a report of a child, 17 months old, who swallowed the drippings from a bottle of fluid extract of eucalyptus. Within a half hour it became drowsy and lost all power in the limbs. The child was pale, its head and extremities were cold, the pupils were contracted, the conjunctivæ were insensitve, the pulse was imperceptible, and the respirations were short and spasmodic. The child could be aroused. Following a soap and lime water emetic, it vomited three times. Whiskey, warm milk and lime water were administered; the child was put to bed and artificial heat was applied. Two and a half hours later, the pulse was feeble and small, but the patient was less drowsy. Castor oil was then administered. The temperature rose, and 36 hours after the ingestion of the eucalyptus had reached 102° F.; the respirations were 60 to the minute. A slight cough and rhonchi were noted. Five days later the child had fully recovered.

CASE III.—Sheaf (1888) reported that a man 25 years old developed vertigo one and one-quarter hours after taking 5 drachms of eucalyptus oil. The patient talked loudly, and exhibited involuntary twitchings of the fingers. He did not vomit. He was conscious two hours later, but the pulse was weak and rapid. Emetics were used and caffeine and sodium salicylate administered. The patient recovered completely.

CASE IV.—Wood (1888) cited a case of Gimbert's: An old man took 80 minims of eucalyptus oil. The power of motion almost disappeared and the patient affirmed that he had lost, for the time being, all sense of the presence of his limbs, so that he was unconscious of them when he shut his eyes. His intellect was perfectly clear throughout.

CASE V.—Wood also stated that Binz had described a similar condition after 75 minims had been taken.

CASE VI.—Neal (1893) reported that a healthy boy, 10 years old, took some eucalyptus ( $\frac{1}{2}$  drachm of blue gum) for prophylactic reasons just before going to bed. In a few moments he was gasping for breath. He vomited and felt much better. Dyspnea became marked, however, one hour later, but no convulsions or diarrhea were noted. The lips and gums were colorless, the chest and neck rigid, and the pulse feeble and rapid. He complained of pain in the right chest, which was relieved by poultices. The intellect remained clear until one hour before death.

At the autopsy, the stomach was found to be much distended with gas, the gastric mucosa being white, thickened, and puckered. There was a quart of fluid in the pleural cavities; the lungs were collapsed, firm and bloodless. The right heart contained frothy liquid blood.

CASES VII AND VIII.—Neal quoted Martindale as having given 80 minims of eucalyptus oil in two and one-half hours. He also mentioned a case in which Croker of Geeling had asserted that a man's death was accelerated by a dose of 1 ounce of eucalyptus.

CASE IX.—Lewin (1897) stated that a boy, 16 years old, after 15 c.c. of the oil, vomited and went into a state of collapse.

Dyspnea and air hunger were noted. The boy died within 15 hours, and at autopsy blood was found in the pleural cavities.

CASE X.—Manquat (1898) speaks of Siegen's case in which the ingestion of 3.5 c.c. of the oil of eucalyptus was followed by headache, drunkenness, stupor, somnolence, weakened reflexes, enfeebled respiration, lowered blood-pressure, decreased temperature, and eventually by paralysis of respiration.

CASES XI AND XII.—Kunkel (1899) describes two cases:

(1) A child, three years old, took a small spoonful of eucalyptus oil. He estimated that the amount was about 8 c.c. Vomiting was followed by speedy recovery.

(2) A boy, 10 years old, took 15 c.c. of eucalyptus oil and died in collapse 15 hours later.

CASE XIII.—Thomas (1899) reports the poisoning of a baby boy, 4 weeks old, with 1 drachm of eucalyptus oil. When seen the patient was comatose; harsh breathing and the odor of the drug on the breath were noted. Ipecac was given and repeated in half an hour. Stimulants were of no avail. Death occurred four hours after the administration of the oil. There was no emesis.

CASE XIV.—Wood (1900) reported that a child three years old grew violently sick within two hours after taking 2 or 3 drachms of the oil. Drowsiness, stupor and collapse developed, along with pin-point pupils. The symptoms lasted 10 hours, but the patient recovered. Except for the absence of stertorous breathing, the condition was described as identical with that encountered in opium poisoning.

CASE XV.—Taylor (1905) stated that a man, 25 years old, took 1 drachm of eucalyptus, and within a few minutes had pain along the œsophagus and in the gastric region. After a time, he became dazed and suffered from a feeling of impending suffocation. He was at first very restless, but later became semicomatose. The pupils were slightly contracted.

Emetics and stimulants were successfully employed, and the following morning the patient was apparently well.

CASES XVI AND XVII.—Benham (1905) reported two cases:

(1) A man, 41 years of age, became comatose after swallowing 1 drachm of the oil. Emetics were successful; the man was entirely well in a few hours.

(2) A young man showed similar symptoms after 1 drachm of the oil. Emetics were employed and the patient recovered.

CASE XVIII.—Smith (1906) investigated a case of poisoning by half a wine-glassful of eucalyptus oil. The particulars concerning the patient are not given, but the oil was a "cineol eucalyptus oil" and a good preparation of the kind.

CASE XIX.—Orr (1906) stated that a boy, two years and nine months old, took 2 drachms of the oil and was seen 15 minutes later. He was in collapse, unconscious, had a very rapid pulse, and his breathing was stertorous. The pupils were contracted to pin-points. He vomited early and was purged. Zinc sulphate was given and was followed by emesis. Whiskey and coffee were then given. One hour later consciousness had returned and the patient was well.

CASE XX.—Benjamin (1906) records the case of a boy, eight years of age, suffering from intermittent fever, who was given 6 drachms of eucalyptus oil at 5 a. m. He vomited half an hour later. At 7 a. m. he became unconscious; vomiting recurred several times before 11 a. m. At this time he was found in partial collapse, the pupils were contracted and the breathing labored. The temperature was 99.8° and the pulse 128. The abdomen was tympanitic. Hiccough was troublesome.

The treatment consisted of cold applications to the head, mustard on the neck, an ammonia mixture internally, and enemata. At 3 p. m. the patient regained consciousness. No after-effects were noted.



CASE XXI.—Myott (1906) observed a man, 34 years old, a heavy drinker, who took 6 drachms of eucalyptus oil. He walked about for two hours, then became dazed and suddenly fell unconscious. Warm water was introduced into the stomach and the patient vomited. Four hours after ingestion of the oil, he was cyanotic and the breathing was labored. Frequent attempts to empty the bronchial tubes of a thin frothy secretion were made. Pulse 128, respiration 24, temperature 97°. Pupils slightly contracted. The patient was then given strychnin and oxygen. The expectoration became thick and blood-tinged, the fever rose continuously, and 40 hours after ingestion, just prior to death, the temperature was 103°, pulse 140, respirations 48. The autopsy showed bulky, heavy lungs, some gastritis and some pleuritis.

CASE XXII.—Schroeder (1908) stated that a child one and one-half years old exhibited evidence of delirium, coma, vomiting and collapse after an unknown dose of eucalyptus. Recovery was complete in a few hours.

CASE XXIII.—Robertson (1909) reported that a man, 55 years old, took 5 drachms of eucalyptus oil before retiring. He awakened during the night feeling sick, but did not vomit until several hours later. He was terribly prostrated, pale grey in color, and cold to the touch. The pulse, however, remained normal in rate and rhythm. The following afternoon he felt fairly well, and he returned to work within a few days.

CASES XXIV AND XXV.—Kirkness (1910) reports two cases:

(1) Man, 28, took between 2 and 3 drachms of eucalyptus oil. Ten minutes later, he suffered from dizziness and from marked dyspnea. The pupils were dilated and the pulse was weak and thready. The temperature sank to between 95° and 96° F. The patient vomited and complained of a sensation of girdle-like constriction. The skin was greenish-yellow. He complained of drowsiness, of great coldness, and of intense frontal and occipital headache. Half an hour after ingestion, marked diarrhœa set in and also frequent and painful micturition. The faces were dark in color and smelled of the oil. He was given emetics and stimulants, was put to bed and was surrounded with artificial heat. This treatment was followed in a few hours by a return of normal temperature and pulse. For three days, however, he looked chlorotic and showed an ataxic gait. The faces, urine and breath all smelled of the oil for a fortnight after the poisoning. Recovery was complete.

(2) A girl of 18 years took 1 ounce of the oil. She complained of intense headache and vomited. She showed collapse, bodily and mentally. The pulse became very feeble, the temperature subnormal, and the pupils dilated. She also complained of a girdle-like constriction. She recovered.

CASE XXVI.—Allan (1910) recorded a case of a child, 20 months old; eucalyptus oil was applied to its chest and 1 ounce of the oil was given by mouth. Within 20 minutes, the child became very sick and seemed to suffer violent pain. A few minutes later, it became semi-comatose and vomited. The pulse was feeble and intermittent, the temperature subnormal; the patient collapsed. Stimulants and artificial heat were employed and two days later the child was reported as well.

CASE XXVII.—Jolly (1910) describes a patient, admitted to the hospital for anemia and dyspepsia, who was found to be suffering from ankylostomiasis. Magnesium sulphate was given at night, followed next morning by eucalyptus oil min. xxx, chloroform 45 min. and castor oil 10 ounces in two doses. Two hours later the patient was weak and giddy, and an hour later in collapse. Langour, giddiness, dyspnea, general pains (most severe in the head, abdomen and urethra) were complained of. The respiration became shallow and labored, the pulse weak and irregular, the blood-pressure low, and the pupils dilated. The breath and skin smelled of eucalyptus. Vomiting did not occur; no urine or

feces passed. Following the application of a mustard plaster over the heart and the administration of strychnine, atropine, artificial heat and enemata, recovery occurred.

CASE XXVIII.—Fogge (1911) reported the case of a boy six years of age, who took 1 drachm of the oil. Four hours later nausea and vomiting occurred, the patient passing into a serious condition of coma and collapse. The case was treated as though it were one of opium poisoning and the recovery was complete.

CASE XXIX.—In 1914, Winterbotham reported a case of poisoning by oil of eucalyptus. The patient, a man 30 years old, took a teaspoonful of "the best eucalyptus extract" at 7 a. m. and another at 10 a. m. He noticed no effect until after luncheon, when (at 1.15 p. m.) he became very pale, began to sweat profusely, and became unable to walk without assistance. He felt drowsy, and retched a little. There was no vomiting and no headache. Winterbotham saw him at 3.30 p. m., and could detect the odor of eucalyptus on his breath. The gait was unsteady. Now and then, his talk was nonsensical. The articulation was impaired. The pulse, though weak, was not accelerated. Alcoholic intoxication was ruled out. At 4 p. m., the patient went to sleep and slept heavily until the next morning when he awoke feeling perfectly well.

Thus, in the above 29 cases, found in the literature, seven ended fatally; all of the other patients appear to have recovered completely within a few days.

Only five cases of the second class of cases could be found; that is, of instances in which the patient responded in an unexpected and unaccountable manner to minute or therapeutic doses. These cases are particularly interesting in relation to the one we report.

CASES XXX AND XXXI.—Galewsky (1905) reported two cases in which a skin disease developed as the result of the patient coming in contact with branches of the eucalyptus tree. He asserted that dermatitis not infrequently results after rubbing eucalyptus oil into the skin and he cited one instance in which an acute papular dermatitis followed its use.

Galewsky states that he was consulted by a woman suffering from erythematous urticaria. She presented large and small urticarial lesions and the intervening areas showed erythematous spots. The itching was intense and the disease was of long duration. The exposed cutaneous surfaces were particularly involved, but the neck and breast also, though to a less degree. She asserted that this rash would entirely disappear when she was away from home for a considerable length of time, but always reappeared on her return. She stated also that the itching was always more severe when she remained for any length of time in one particular room. Galewsky visited her home and in the above-mentioned room he found branches of the eucalyptus used as an ornament. Thinking that this might possibly be the etiological factor, he ordered it removed. The housemaid scoffed at this idea and to prove the harmlessness of the eucalyptus, moistened some of these leaves and rubbed them on her own skin. At the end of half an hour she exhibited lesions identical with those complained of by her mistress. The eucalyptus was removed and subsequently both patients fully recovered, the rash never reappearing.

CASE XXXII.—Davies (1906) stated that his son fainted on inhaling the vapor of eucalyptus and that on another occasion he had to leave a chapel during service on account of a threatened fainting spell brought on by the odor of eucalyptus, the leaves being used in the way of decoration. This peculiarity is stated to be inherited from the mother who also faints on smelling eucalyptus.

CASE XXXIII.—Hans Vörner (1907) reported an experience with eucalyptus which proves conclusively that in certain persons

it can produce skin lesions. In August, 1906, a patient entered the skin clinic and stated that for two days he had been taking 20 drops of eucalyptus oil and that, after doing so, he had developed a skin rash which itched and burned. He ascribed this to the eucalyptus. On examination, it was found that wheals were present over the entire cutaneous surface. They were chiefly discrete, but in places were confluent. The single lesions varied from 2 mm. to 2 cm. in diameter, while the confluent lesions were in some areas as large as one's hand. They were of a livid red color, the center sometimes slightly blue, and the edges a more intense red. The oil was stopped and the rash promptly disappeared. In order to test the assertion of the patient, the oil was administered again 10 days later, whereupon an identical rash appeared within 24 hours.

Six weeks later the rash reappeared without any oil having been administered. The patient complained, however, of a cold in the head, of headache, and of an intense taste of eucalyptus oil. Identical attacks recurred in November and again in December. For two or three months he remained free, but similar attacks occurred again in March and again in April, but the taste of oil was not present in these last two attacks.

During the various attacks the back of the head, the back, abdomen, right breast, arm, thigh and legs were all involved, the hands and feet escaping altogether except for a lesion on one thumb during one of the attacks.

CASE XXXIV.—Oppenheim (1912) reported that a tailor, 36 years of age, complained of skin lesions developing as the result of taking cough lozenges ("*Huste nicht*"). The backs of the hands, palms, fingers, wrists, and dorsa of the feet showed an eruption, consisting of pea-sized, bright red, cherry-red and brownish-red papules and nodules. These were mostly circumscribed, but were confluent on the fingers and toes, and on the palms and soles of the feet. The color did not disappear on pressure with the glass slide. Hemorrhages appeared here and there. There was no desquamation. The mucous membranes were not involved. Slight itching was associated with the eruption. The color changed later to brown. The rash was preceded by anorexia, insomnia, malaise and fatigue, those symptoms appearing two hours after the last tablet was taken.

#### DISCUSSION

From the preceding analysis, at least two different syndromes emerge as evidences of intoxication with derivatives of myrtaceous plants (eucalyptus oil, myrtol, cineol, etc.), and we shall venture to designate them respectively as (1) a myrtogenic neuropathy and (2) a myrtogenic dermatopathy, though without prejudice as to whether the terpenes in the oils are the toxic agents or some chemical substance that accompanies them. The dermatopathy may in some of the cases be a special instance of the neuropathy, through the mediation of the autonomic nerves innervating the blood vessels of the skin, though a true dermatitis seems certainly to have been present in other cases.

(1) *The Myrtogenic Neuropathy*.—In the cases discovered in the literature, the first 29 grouped as Class I (*vide supra*) appear to belong to this category. In a few minutes, or a few hours, after the ingestion of a considerable quantity of the myrtaceous derivatives mentioned, the patients became seriously ill. They were pale, dyspnoic, and restless and complained of headache, dizziness, twitchings, and of pains (in the chest or limbs). At first, the intellect was sometimes

clear, but, in many instances, the patients soon became drowsy and complained of feeling dazed and of a loss of knowledge of the whereabouts of their extremities. On attempting to walk, they staggered about and sometimes fell. Some patients stated that they felt a girdle-sensation (constriction). In the severer intoxications, they were delirious or suffered from convulsive seizures, and some became comatose, with pronounced symptoms of collapse (tachycardia, arterial hypotension, pallor and slight cyanosis, cold extremities, diminished reflexes, hypothermia). Vomiting and diarrhoea were common accompaniments of the intoxication. It is fortunate when these symptoms occur, and if vomiting does not occur spontaneously, it should be induced, or the stomach should be washed out to prevent further absorption of the poisonous substance.

The behavior of the pupils has been variable; in most cases, there was extreme myosis; in some instances, outspoken mydriasis was observed. It seems likely that the myosis indicates an irritation of the midbrain autonomic system, the mydriasis a paralysis of the same. In the domain of the pelvic division of the cranio-sacral autonomic system, the patients sometimes complained of pollakiuria and of dysuria.

The pleural effusion reported in two of the cases deserves especial mention; in Neal's case, a quart of fluid was found in the pleural cavities; in Lewin's case, a bloody effusion was observed. Whether these pleural phenomena were accidental accompaniments, or were actually due to the intoxication, must be left to later studies to decide.

Several observers have been struck with the resemblance to poisoning by opium, but they emphasize the absence of the stertorous breathing that accompanies that intoxication.

(2) *The Myrtogenic Dermatopathy*.—In four cases in the literature, and in the case we report ourselves, remarkable cutaneous manifestations followed the ingestion of myrtaceous derivatives. In our own case, the skin lesions were associated with marked nervous symptoms (great depression; symptoms of collapse).

The lesions in the skin vary in their nature. Sometimes merely (1) *erythematous*; sometimes they are (2) *urticarial* in type; and sometimes there is (3) an outspoken dermatitis.

#### CONCLUSIONS

(1) Derivatives of plants belonging to the natural order *Myrtaceæ*, and especially oil of eucalyptus and myrtol, may in large doses cause profound intoxication. In certain persons, there is an idiosyncrasy, the symptoms of intoxication occurring after minute or therapeutic doses.

(2) The intoxication may affect chiefly the nervous system (*myrtogenic neuropathy*) or chiefly the skin (*myrtogenic dermatopathy*); in some persons, nervous and cutaneous manifestations are simultaneously observable.

(3) Recovery occurs in most instances, though several fatalities following eucalyptus poisoning have been reported.

(4) The symptoms of intoxication of the nervous system observed in man can be reproduced in animals by subcutaneous and by intraperitoneal administration of myrtol.

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## DAKIN'S SOLUTION AND DAKIN'S OIL IN THE NORMAL PERITONEAL CAVITY OF THE DOG

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The following observations are reported in order to draw attention to the fact that the indiscriminate use of the chlorin antiseptics is not entirely devoid of danger. It must be emphasized, however, that in presenting them no criticism is suggested regarding the Carrel-Dakin method of wound treatment or the use of Dakin's oil, inasmuch as clinical experience abroad, in The Johns Hopkins Hospital and in certain other institutions in this country, has shown the importance of these antiseptics in combating infections.

The remarkable results from the use of the normal solution of chlorinated soda reported by Carrel,<sup>1</sup> and from the use of the dichloramine-T oil reported by Lee and Furniss<sup>2</sup> suggested these agents in certain infections of the pleural and peritoneal cavities. Sufficient time has elapsed now since the introduction of the chlorin antiseptics in the treatment of empyema to justify the conclusion that both agents may be used with safety in an infected pleural cavity. The evidence at present, however, regarding the reaction of the infected peritoneum to Dakin's solution and to dichloramine-T oil, is much less definite.

The question as to whether a particular germicide should be used in infections of the serous cavities, of course, may be

settled more or less satisfactorily either by observing the effects resulting from the use of the antiseptic in selected clinical cases or by studying the reaction of animals injected with it under varying conditions. The latter method has the disadvantage that it is difficult, in fact often impossible, to reproduce the same pathological process in animals. This means that the conclusions drawn from animal experiments must be used with a considerable amount of reservation when they are applied to clinical work. Laboratory experiments, nevertheless, may be of great service in working out problems of this nature, since it is only by experimenting with animals that we may determine how the normal serous membranes will react to a given chemical agent.

With this idea in mind certain problems were studied in the laboratory shortly after the introduction of the Carrel-Dakin method of wound treatment into this hospital, and again later when the dichloramine-T oil technique was adopted for suitable cases. The excellent results obtained with the chlorin antiseptics suggested to Dr. Halsted several possible uses for them in appropriate cases of intra-abdominal infections. In the following paragraphs a brief review of the experiments will be outlined.

Dogs apparently in good health were used throughout the work. The solutions of chlorazene were obtained by dissolving the commercial tablets (Abbott) in sterile water. The hypochlorite solution (Dakin's solution) came from the hospital pharmacy. A fresh preparation was made each day. In all

<sup>1</sup> Carrel, Dakin, Daufresne, Dehelly et Dumas: Traitement abortif de l'infection des plaies, *La Presse méd.*, 1915, XXIII, 397.

<sup>2</sup> Lee, W. E., and Furniss, W. P.: The Use of Dichloramine-T in the Treatment of Infections and Infected Wounds, *Ann. Surg.*, 1918, LXVIII, 14.



of the experiments with Dakin's oil a 5 per cent solution of dichloramine-T in chlorinated paraffin oil (chlorcosane) was used.

In the first series a solution of chlorazene was injected into the peritoneal cavity with a Record syringe. One animal weighing 17 pounds received 30 c. c. of a .5 per cent solution. Forty-eight hours later the dog was active and ate well. When the abdomen was opened, however, about one and a half ounces of grayish-colored, free fluid were discovered. There was a moderate and general congestion of the peritoneal surfaces with a rather marked deposit of fibrin on the viscera in the part of the cavity which was nearest to the point of injection.

Another dog (weight 21½ lbs.) received 20 c. c. of a 1 per cent solution. Eleven days later it died and at necropsy the abdomen was found to be full of fluid. Fibrin was present in large amounts. Throughout the four quadrants, but particularly in the upper two, loops of bowel were glued together by the exudate. Both the parietal and the visceral peritoneal surface were greatly altered in appearance.

The results in another dog (weight 56 lbs.) may be mentioned. In this case 90 c. c. of a 1 per cent solution were injected intraperitoneally. Six days later the abdomen was opened under aseptic precautions. About 250 c. c. of cloudy, blood-stained, free fluid were found. A considerable amount of fibrin was present, and the peritoneal surfaces were thickened and deep red in color.

Practically all of the fluid was removed and the wound closed. The animal made a rapid recovery and 16 days later when the viscera were again inspected almost nothing was found to supply evidence of the former inflammatory changes. The dog undoubtedly would have died had the fluid not been removed, as clinically it showed a progressive loss of appetite and strength up to the time of the first exploratory operation.

In the second series Dakin's solution was used. No animal succumbed to the effects of the fluid injected in amounts less than 30 c. c. One dog (weight 15½ lbs.) received 30 c. c. intraperitoneally, and at the end of the following week it was active and had a good appetite. An exploratory incision, made eight days after the injection, revealed only a few cubic centimeters of free fluid. There was still a slight congestion of the visceral peritoneal surfaces. A few traces of old fibrin were evident at certain points. The picture at this time was not far from the normal; it indicated, nevertheless, that there had been a marked reaction to the injection. The cause of death remained obscure.

Into another dog (weight 18 lbs.) 90 c. c. were injected intraperitoneally. Fluid rapidly accumulated and death occurred on the eighth day. The pathological picture was similar to that noted in some of the fatal cases described above. Larger amounts of the neutral solution of chlorinated soda led to a more rapid exitus with extensive peritoneal changes.

A striking feature of an injection performed without anesthesia was the evidence of severe abdominal pain. A few cubic centimeters of the fluid sufficed to cause marked abdominal

rigidity, extensor spasms of the leg muscles, involuntary defecation and urination, and extreme restlessness.

Approximately similar results from the injection of Dakin's solution into the normal peritoneal cavity have been reported recently by Mann and Crumley.<sup>2</sup>

In a third series of animals an attempt was made to determine how the normal gall-bladder and common bile-duct would react to an injection of Dakin's solution. One experiment consisted of exposing the gall-bladder under aseptic precautions and aspirating all of the bile with a Record syringe. Through the same needle-hole the bladder was then distended with Dakin's solution (60 c. c. were used) after which the puncture wound was closed with fine silk stitches. This animal was in excellent condition several days later. An exploratory incision made 4 days after the operation disclosed no evidence of peritoneal reaction.

In a number of other dogs a fistula was established between the gall-bladder and the skin by transplanting a piece of jejunum (measuring about 7 cm. in length) with its blood supply intact, in such a way that one end opened into the gall-bladder and the other upon the surface of the abdomen. After the wounds had healed Dakin's solution was injected into the gall-bladder through the intestinal lumen. No deleterious effects were ever noted subsequent to such injections.

A fourth series of experiments was carried out more recently with Dakin's oil. One dog (weight 22 lbs.) received 11 c. c. intraperitoneally. There was an immediate reaction to the oil. The animal became restless and when placed on the floor a marked, cat-like arching of the spine was noted together with an extensor rigidity of the hind legs. About half an hour later it vomited and gave evidence of much abdominal discomfort. The animal died 26 days after the injection, greatly emaciated. Following the introduction of the oil the dog continued to remain quite ill. There was marked weakness together with anorexia and some vomiting. At autopsy no signs of an active inflammatory process were evident, but there was ample evidence that a very extensive process of this nature had existed in the near past. The loops of intestine were inextricably matted together, and in the vicinity of the site of the injection there was an indurated mass which suggested an old inspissated abscess.

Into the peritoneal cavity of another dog (weight 20½ lbs.) 20 c. c. of the oil were injected. The animal died during the following night and when the abdomen was opened a typical picture of extensive peritonitis appeared. Besides the free fluid, the fibrin and the congestion of the peritoneum, there was a perforation with ragged necrotic edges on the anterior surface of the stomach. Most of the oil injected had come in contact with this region first.

In order to ascertain the effects of the oil upon the gall-bladder and common duct all of the bile was aspirated from the bladder and a corresponding quantity (16 c. c.) of

<sup>2</sup>Mann, F. C., and Crumley, W. G.: Neutral Solution of Chlorinated Soda (Dakin's solution) in the Normal Peritoneal Cavity, *Jour. Amer. Med. Assoc.*, 1918, LXX, 840.

the dichloramine-T was then injected into it. The needle-hole was closed with fine silk stitches. Two days later the dog appeared to be normal in every way. The animal was sacrificed on the 43d day and on examination gave no evidence of an old peritonitis. Both the common duct and the duodenal mucosa were natural in appearance. The gall-bladder, however, was shrunken and contained some thick, yellowish mucus.

In the concluding experiments Dakin's oil was injected into the right pleural cavity. One dog (weight 45 lbs.) received 16 c. c. No anesthesia was used. There was an immediate and marked reaction—restlessness, evacuations of the bladder and rectum, muscular spasm of the abdomen, and a certain degree of extensor rigidity of the legs. The animal was placed on its feet after the injection but soon fell to the floor. It died with symptoms of respiratory failure  $2\frac{1}{2}$  minutes after the first few cubic centimeters of oil had been injected. When the thorax was opened, several large, dry, whitish areas on the pleura were found, which suggested in a way superficial silver nitrate burns. The oil lay at the bottom of the cavity. The clinical course here strongly reminded one of the pleural reflex deaths described particularly by French writers.

Ten cubic centimeters of the oil were injected into the pleural cavity of another dog of about the same weight. In this instance the animal was anesthetized. No unusual symptoms marked the convalescence, and the animal remained apparently in good health.

#### CONCLUSIONS.

Both the neutral solution of chlorinated soda (Dakin's solution) and dichloramine-T in chlorinated paraffin (Dakin's oil), when injected into the normal peritoneal cavity of a dog, lead to an inflammatory reaction, the degree of which is directly proportional to the amount of chlorin antiseptic used. With a sufficient quantity (less of the oil suffices) death ensues.

When either of the chlorin antiseptics is injected into the gall-bladder of a dog no abnormal symptoms appear. Following the injection of the oil, however, the gall-bladder becomes thickened and shrunken, though the remainder of the biliary tract shows no discernible changes.

A small amount of Dakin's oil, when injected into the normal pleural cavity of an unanesthetized dog, may lead to a rapid (reflex?) death.

Since Dakin's oil, particularly, has been used without recognizable ill effects in certain infections of the abdominal cavity, the results from the experiments outlined above suggest that the wall of an abscess cavity or sinus must play an important part in protecting the peritoneum in general from the effects of the free chlorin. They also suggest that the maintenance of an adequate drainage tract is an indispensable part of the technique for using antiseptics of this nature within the abdomen. Until more evidence is at hand, then, both of the chlorin antiseptics should be used in intra-abdominal infections with caution and certainly only in carefully selected cases.

## MULTIPLE PRIMARY MALIGNANT TUMORS WITH REPORT OF A CASE OF CARCINOMA AND SARCOMA IN THE SAME INDIVIDUAL

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The presence of multiple tumors in the same individual has been for many years a subject of much interest. It was early noted and subsequently emphasized that with certain kinds of tumors the tumor formation was more often multiple than single. Virchow (182) called attention to the presence of multiple fibromata of the skin and v. Recklinghausen (187), with whose name this condition has been since associated, made extended studies of this disease. These two observers also noted that such multiple tumors sometimes underwent malignant degeneration and were transformed into sarcomata. Later, similar cases were reported by Genersich (54), de Morgan and Coupland (115), Westphalen (191), and others. Another well-known type of multiple tumors is that of multiple lipomata which have been studied especially by Meerbeck (110), Blaschko (21), Petren (128), Weil (192), and Lyon (105). In addition to these examples it has been noted that certain other benign tumors such as angiomas may be often multiple, and a patient may have angioma of the liver, adrenals, ovaries and uterus, as in a case reported by Payne (125).

The presence of multiple malignant tumors is, however, comparatively uncommon and the following case is reported as an example of this interesting condition.

Mrs. H. G. age 60 years was admitted to the Bell Memorial Hospital April 19, 1915 suffering with a tumor on the face. This growth, which involved the right side of the nose and extended to the inner canthus of the right eye, had been present for several years and was growing slowly (Fig. 1). The clinical diagnosis of rodent ulcer was made and X-ray treatments of the growth instituted. While in the hospital the patient complained a great deal of headache, had little appetite and at times talked irrationally. Death occurred rather unexpectedly on May 22, 1917, and the autopsy was performed two hours later.

The autopsy showed a marked bronchopneumonia of both lungs, a generalized arteriosclerosis and extensive scarring of both kidneys. The most interesting findings were those in the stomach. The wall of the stomach was markedly thickened throughout, had a whitish semi-translucent appearance and cut easily. At the cardia of the stomach there was a large polypoid

growth which showed some areas of ulceration on the surface. This mass also had ulcerated through the wall of the stomach in one place, forming a sinus which passed by the spleen and through the diaphragm to the base of the left lung where it was closed by dense adhesions. No metastases were noted.

The microscopic examination of the tumor in the stomach shows it to consist of masses of round cells, presenting no especial arrangement and showing a small number of connective-tissue fibrils (Fig. 2). Microscopic sections of the tumor of the face show it to be composed of large atypical epithelial cells arranged in nests and strands. In some areas there are epithelial pearls present and evidence of infiltration downward (Fig. 3).

The gross and microscopic evidence in this case shows that we are dealing with an example of two quite different types of malignant tumors in the same individual—a carcinoma of the face and a round-celled sarcoma of the stomach.

The presence of two primary malignant growths in the same person was at one time considered extremely rare, Orth stating in 1895 (123) that he had never seen a carcinoma and a sarcoma in the same individual. In 1896 Walter (184) collected six cases in each of which the two tumors were of different types. Wells (190) in 1901 collected 17 cases of multiple primary tumors and three cases of tumors composed of transformed epithelium and mesoderm in the same organ, the so-called carcinoma sarcomatodes. Wooley (195) in 1903 collected 26 examples of multiple primary carcinomata, five of multiple primary sarcomata and four cases of multiple malignant growths of more than one type. Theilhaber and Edelberg (173) in 1912 made a very extensive study of multiple primary carcinomata, collecting 44 examples of multiple carcinomata in the same system of organs and 41 cases of multiple carcinomata in various organs. Bartlett (9) in 1914 in an excellent article on the subject states that he has reviewed 95 cases of multiple primary tumors. All of these observers, however, have emphasized the comparative rarity of the condition, although statistics upon this point show some variation. Reichmann (139) in 711 necropsies found two examples, Redlich (138) in 507 cases saw two, Goetting (56) in 1000 post-mortems found only two instances.

Some observers, notably Walter (184), Wooley (195), and Adami (3), attach much importance to the occurrence of multiple primary tumors as shedding some possible light upon the etiology and distribution of malignant tumors, whereas other investigators, notably Wells (190), considered them more in the light of a coincidence. In order to assist in the understanding of this interesting problem, a collection of cases has been made and the various facts as to the location, number, and nature of the tumors considered.

In all 628 examples of multiple primary tumors have been reviewed. The greatest number of these cases, 389, were examples of multiple carcinomata in the skin, in the same organ or in each of a pair of organs. This group of tumors has been thoroughly studied by Theilhaber and Edelberg (173) and as their tables are so comprehensive no attempt has been made to add to their collection.

Tabulations of carcinomata in different organs but belonging to the same system show 43 examples, while carcinomata in various organs not members of the same system of organs were present in 53 instances. In all then 485 instances of multiple primary carcinomata were collected.

The number of instances in which examples of different types of tumors were found in the same person was much smaller. One hundred and twenty-three such cases were noted, in 66 of which the tumors were in the same organ, in nine they were in organs belonging to the same system and in 48 cases the different tumors were located in various organs. In this group it is of interest to note that in over one-half of the cases (54 per cent) the different types of tumors were located in the same organ. The uterus was the most common seat of two tumors of different types, being represented by 22 instances, followed by the breast and the thyroid gland, each showing 10 examples.

The most common combination of different types of malignant tumors was that of carcinoma and sarcoma. Ninety-two instances of this combination were noted, 62 or 75 per cent of which were located in the same organ, seven were located in the same system and 23 in different organs.

The presence of both carcinoma and sarcoma in the same organ has led to much discussion especially since the work of Virchow\* who laid stress upon the carcinoma sarcomatodes, a tumor in which both carcinomatous and sarcomatous elements are present.

Wells\* until 1901 found only three undoubted instances of such tumors. A large number have been described since that time, but these figures have been greatly reduced by Herxheimer (70) who states that the actual number of cases of true carcinoma sarcomatodes reported up to 1908 was 20. Herxheimer pointed out that many cases reported in the literature as instances of carcinoma sarcomatodes are really examples of two distinct tumors, a carcinoma and a sarcoma in the same organ. Saltykow (150) in 1914 stated that there were 25 authentic cases reported in the literature to which number he added three. In our table, because of the difficulty of separating them, the cases of carcinoma sarcomatodes are included with those in which a carcinoma and a sarcoma were present as distinct tumors in the same organ.

This brief summary of the cases of multiple primary tumors would seem to indicate rather clearly that no single explanation suffices in all cases and that although some instances may be explained as simple coincidences, in certain others deeper causes are at work.

In the examples of multiple primary carcinomata of the same organ or of adjacent organs we are probably dealing with two factors—transmission by infection and multiple origin of tumors. Many cases are now on record indicating that contact may spread a carcinoma from a primary growth to an adjacent organ. Such tumors have been described especially in the skin and Borrmann (24), who has devoted much study to this problem, although believing that the number of cases

\* Loc. cit.



of transplantation carcinomata (Impfkarzinome) has been exaggerated, yet admits its occurrence. This group of cases, although many of such growths are often apparently secondary to a primary tumor, are in many instances possibly not ordinary true metastases, since the transference of the growth may conceivably be accomplished in some other manner than by an actual implantation of tumor cells.

The multiple origin of carcinomata is now, since the work of Peterson (126) and of Hauser (67) a well-established fact. Both of these observers have shown that carcinomata may arise simultaneously from several centers of origin. While disagreeing as to the relative frequency of the "unicentric" and "multicentric" mode of origin, both agree that the "multicentric" mode does occur. Thus a carcinoma may, like an abscess, arise as a single large lesion, or it may be formed by coalescence just as a number of small abscesses may fuse to form a larger lesion; or again the multiple carcinomata may remain discrete just as we often observe multiple small abscesses. Some of the most striking examples of the multicentric origin of malignant tumors are those in which a certain number of polypi, in cases of multiple polyposis of the stomach and intestine, become malignant and are transformed into carcinomata. Ribbert (142) has collected 30 such cases.

The presence of different types of tumors in the same organ such as a carcinoma and a sarcoma, or the presence of a mixed type as the carcinoma sarcomatodes, while often regarded as a mere coincidence, has taken on an added interest and importance since the oft-quoted work of Ehrlich and Apolant (40). These two observers by repeated inoculation of a typical adenocarcinoma in mice succeeded in changing it first into a mixed tumor, and later into a typical sarcoma. Russell (148) has reported an adenocarcinoma of the breast in a mouse, which after continuous growth in the animal gradually became sarcomatous and later became a pure sarcoma. This change of the carcinoma into a sarcoma in Russell's case seems to be controlled entirely by the time element, since if the transplanted carcinoma is removed early and transmitted to another animal, carcinoma results, whereas if the transplanted carcinoma is allowed to grow until it becomes a sarcoma, all animals then inoculated develop a pure sarcoma.

These experimental findings combined with clinical observations suggest very strongly that the presence of a carcinoma and sarcoma in the same organ is due to some abnormal stimulus which acts upon both epithelial and mesodermal elements, producing either both epithelial and mesodermal tumors or a single tumor showing both types of cells, as in the carcinoma sarcomatodes. Similar influences are probably at work in such cases as that reported by Kidner (83) where the removal of a sarcoma was followed later by the appearance of a carcinoma at the site of the old operation.

Our statistics show that the multiple tumors do not have a predilection for organs of the same system excluding paired organs, which is in marked contrast to their predilection for a single organ. We have found multiple tumors—both carcinomata and tumors of different types—more common in organs not related by any system. The occurrence of multiple

tumors in various organs cannot be readily explained, but here again the assumption of more than a mere coincidence would seem to be justified in many instances. The susceptibility of individuals of certain families to malignant tumors such, for instance, as those related by Vander Veer (180), is an old clinical observation, which seems now to be placed upon a firm base by the brilliant breeding experiments of Slye (164). She has shown that mice with a cancerous ancestry have a marked tendency to develop spontaneous cancers, and also that mice with such ancestry develop carcinomata readily as the result of a trauma which in control animals having a non-cancerous ancestry produces no such results. The suggestion here is rather strong that individuals developing multiple malignant tumors have some sort of a susceptibility to tumors which is not limited to any one organ or region of the body.

There must also be mentioned the possibility that in a few of the cases we are dealing not with multiple primary tumors, but with a carcinoma, the metastases of which simulate very closely sarcomata. Such instances have been reported by Polano (132). The number of such cases, however, is probably very small.

Nine examples of three primary multiple tumors were noted and two examples of four tumors occurring simultaneously. The case of Lewis (100) is unique; he reported nine different tumors in the same patient, while that of Sliwinsky (163) who described seven is equally interesting.

In our own case it is difficult perhaps to draw any very definite conclusions from the presence of two distinct and different tumors. They might be regarded simply as a coincidence, although the case would seem to be equally well explained by the assumption that the patient was predisposed to cancer and that subsequent irritation in two organs produced malignant growths in both of them. A great variety of combinations of two different tumors are obviously possible, but this is the only instance noted in which the combination of a carcinoma of the face with a sarcoma of the stomach occurred.

#### MULTIPLE CARCINOMATA IN THE SAME SYSTEM OF ORGANS

Abesser	(2)	Carcinoma of jejunum, carcinoma of tongue.
Beadles	(10)	Carcinoma of breast, epithelioma of cervix.
"		Carcinoma of breast, epithelioma of vulva.
Besche	(17)	Carcinoma of jejunum, carcinoma of colon.
Böckel	(22)	Carcinoma of uterus, carcinoma of breast.
Borchhardt	(23)	Carcinoma of stomach, carcinoma of colon.
Bucher	(27)	Carcinoma of stomach, carcinoma of descending colon.
Devis	(37)	Carcinoma of pylorus, carcinoma of rectum.
Eichbaum	(41)	Carcinoma of esophagus, carcinoma of stomach.
d'Erchia	(44)	Adenocarcinoma of labia, squamous-celled carcinoma of cervix.
Feilchenfeld	(45)	Carcinoma of stomach, carcinoma of rectum.
"		Carcinoma of stomach, carcinoma of gall-bladder.
"		Carcinoma of stomach, carcinoma of duodenum.
Frangenheim	(50)	Squamous-celled carcinoma of gum, mucoid carcinoma of ileum.

Götting	(56)	Squamous-celled carcinoma of larynx, adenocarcinoma of rectum, medullary carcinoma of stomach.
Hansemann	(65)	Carcinoma of esophagus, carcinoma of stomach.
"		Carcinoma of tongue, carcinoma of esophagus.
Hauser	(67)	Adenocarcinoma of rectum, medullary carcinoma of stomach.
Hofbauer	(73)	Papillary carcinoma of Fallopien tube, squamous-celled carcinoma of cervix.
Israël	(75)	Carcinoma of tongue, carcinoma of jejunum.
Kaufmann	(79)	Carcinoma of breast, carcinoma of ovary.
Keding	(81)	Carcinoma of esophagus, carcinoma of stomach.
Klebs	(84)	Carcinoma of left breast, carcinoma of left ovary.
Lamnois	(98)	Carcinoma of stomach, carcinoma of duodenum.
Mandry	(107)	Carcinoma of thigh, carcinoma of leg.
"		Carcinoma of breast, carcinoma of ovaries.
Michelsohn	(112)	Carcinoma of breast, carcinoma of uterus, adenocystoma of ovary.
Nehrkorn	(117)	Carcinoma of breast, carcinoma of uterus.
Ogata	(121)	Carcinoma of esophagus, carcinoma of stomach.
Pignal	(131)	Carcinoma of esophagus, carcinoma of stomach.
Pirscher	(130)	Carcinoma of uterus, carcinoma of ovary.
Ravenna	(136)	Carcinoma of esophagus, carcinoma of colon.
Reutter	(140)	Carcinoma of esophagus, carcinoma of stomach.
Richter	(143)	Carcinoma of breast, carcinoma of uterus.
"		Carcinoma of ovary, carcinoma of intestine.
Rosenbach	(145)	Squamous-celled carcinoma of esophagus, adenocarcinoma of pylorus.
v. Scheel	(153)	Carcinoma of stomach, carcinoma of liver.
Simon	(163)	Carcinoma of bladder, carcinoma of kidney pelvis.
Sumpter	(168)	Carcinoma of right ear, carcinoma of left ear.
Taylor	(171)	Adenocarcinoma of uterus, carcinoma of both ovaries.
Walter	(184)	Carcinoma of breast, carcinoma of uterus, adenocystoma of ovary.
Warthin	(187)	Adenocarcinoma of intestine, adenocarcinoma of gall-bladder.
Winiwarter	(194)	Carcinoma of right side of tongue, carcinoma of left side of mouth.
Wehmer	(188)	Carcinoma of body of uterus, adenocarcinoma of ovary.
Wooley	(195)	Mesotheliomata of both adrenals.

## MULTIPLE CARCINOMATA IN VARIOUS ORGANS

Altschul	(5)	Carcinoma of lower lip, carcinoma of hands, colloid carcinoma of cecum.
"		Squamous-celled carcinoma of bladder, adenocarcinoma of stomach.
Beck	(13)	Epithelioma of uterus, cancer of colon.
Becker	(14)	Carcinoma of eyelid, carcinoma of ear.
Besche	(17)	Carcinoma of lip, carcinoma of penis.
"		Carcinoma of face, carcinoma of stomach.
"		Carcinoma of lip, carcinoma of rectum.
deBeurmann	(18)	Carcinoma of face, carcinoma of pylorus.
Bryant	(26)	Carcinoma of nose, carcinoma of breast.
Chiari	(30)	Carcinoma of colon, carcinoma of vulva.
Chilesotti	(31)	Carcinoma of neck, carcinoma of lumbar region.

Cordes	(33)	Carcinoma of foot, adenocarcinoma of stomach.
Cullen	(34)	Squamous-celled carcinoma of skin, adenocarcinoma of prostate (dog).
Deetz	(36)	Squamous-celled carcinoma of gall-bladder, carcinoma of rectum (cylindrical-celled) dermoid of ovary.
Feilchenfeld	(45)	Carcinoma of stomach, carcinoma of breast.
Fraenkel	(48)	Carcinoma of breast, carcinoma of intestine.
Graviller	(57)	Carcinoma of lip, carcinoma of breast.
Hansemann	(65)	Carcinoma of stomach, carcinoma of bronchi.
"		Carcinoma of stomach, carcinoma of ovary.
Hauser	(67)	Carcinoma of ear, carcinoma of pylorus.
Herschel	(68)	Carcinoma of skin, carcinoma of esophagus.
Herxheimer	(71)	Carcinoma of cheek, carcinoma of liver.
Hutchinson	(74)	Carcinoma of face, carcinoma of breast.
Kaufmann	(79)	Carcinoma of eye, carcinoma of hand.
Klebs	(84)	Carcinoma of eyelid, carcinoma of rectum.
Krönig	(91)	Carcinoma of stomach, carcinoma of uterus.
Kuster	(94)	Carcinoma of nose, carcinoma of breast.
Lubarsch	(104)	Carcinoma of breast, carcinoma of stomach.
"		Carcinoma of uterus, carcinoma of stomach.
Michelsohn	(112)	Carcinoma of nose, carcinoma of breast.
Nehrkorn	(117)	Carcinoma of bladder, carcinoma of anus.
Pusateri	(113)	Adenocarcinoma of breast, carcinoma of stomach.
Richter	(143)	Adenocarcinoma of thyroid, carcinoma of ovary.
Redlich	(138)	Carcinoma of lung, carcinoma of ileum.
"		Carcinoma of colon, carcinoma of ovary.
Reutter	(140)	Carcinoma of stomach, carcinoma of uterus.
Schwarz-		
waller	(160)	Carcinoma of labia, carcinoma of breast.
Schweden-		
berg	(161)	Carcinoma of colon, carcinoma of breast.
Tannberg	(170)	Carcinoma of duodenum, carcinoma of bladder.
Tixier	(176)	Carcinoma of larynx, carcinoma of thyroid.
Tsuji	(177)	Carcinoma of nose, carcinoma of uterus.
Turner	(178)	Carcinoma of lip, carcinoma of penis.
VanderVeer	(180)	Carcinoma of breast, epithelioma of skin (of breast).
Venulet	(181)	Adenocarcinoma of thyroid, carcinoma of uterus.
"		Adenocarcinoma of stomach, carcinoma of lip.
"		Adenocarcinoma of stomach, carcinoma of uterus.
Volkman	(183)	Carcinoma of skin of buttocks, carcinoma of rectum.
Warthin	(187)	Adenocarcinoma of ovary, colloid carcinoma of gall-bladder.
Winiwarter	(194)	Carcinoma of both breasts, carcinoma of jejunum.
"		Carcinoma of lower lip, carcinoma of glabella.
"		Carcinoma of tongue, carcinoma of scar in skin.
"		Carcinoma of nose, carcinoma of stomach.
"		Carcinoma of ear, carcinoma of stomach.
Ziba Shin-Iz	(196)	Carcinoma of esophagus, carcinoma of larynx.
"		Squamous-celled carcinoma of esophagus, adenocarcinoma of trachea.

## DIFFERENT TUMORS IN THE SAME ORGAN

Albrecht	(4)	Carcinoma sarcomatodes of uterus.
Ballin	(7)	Carcinoma sarcomatodes of uterus.
Becker	(14)	Melanotic sarcoma and carcinoma of the face.
Behrendsen	(16)	Cholesteatoma of pons, glioma of left cerebral hemisphere.

Benthin	(15)	Carcinoma sarcomatodes of uterus.
Coenen	(32)	Carcinoma and sarcoma of breast.
Dorsch	(38)	Carcinoma and sarcoma of breast.
Emanuel	(43)	Carcinoma and sarcoma of uterus.
Forster	(46)	Carcinoma and sarcoma of thyroid.
Fraenkel	(48)	Carcinoma sarcomatodes of uterus.
Fraugenheim	(50)	Carcinoma and sarcoma of esophagus.
v. Franqué	(51)	Adenocarcinoma of cervix and round-celled sarcoma of body of the uterus.
Gebhard	(52)	Carcinoma and sarcoma of uterus.
Gliniski	(55)	Adenocarcinoma and sarcoma of uterus.
Haenel	(62)	Sarcoma and neuroganglioma of brain.
Hansemann	(65)	Carcinoma sarcomatodes of gall-bladder.
Herxheimer	(70)	Carcinoma sarcomatodes of esophagus.
Iwanoff	(76)	Carcinoma and sarcoma of uterus.
Kahler	(77)	Carcinoma sarcomatodes of pharynx.
Kaufmann, E.	(78)	Carcinoma sarcomatodes of breast.
"		Chondro-carcino-sarcoma of breast.
Kaufmann, C.	(80)	Carcinoma and sarcoma of thyroid.
Kettle	(82)	Carcinoma and sarcoma of breast.
Klein	(85)	Carcinoma and sarcoma of uterus.
Klein, H.	(86)	Carcinoma sarcomatodes of nasal sinuses.
Kocher	(87)	Adenocarcinoma, spindle- and giant-celled sarcoma of thyroid.
Krompacher	(90)	Carcinoma and sarcoma of bladder.
"		Carcinoma and sarcoma of mouth.
"		Carcinoma and sarcoma of breast.
Kubinyi	(92)	Carcinoma and sarcoma of uterus.
Kummer	(93)	Carcinoma and sarcoma of thyroid.
Landsteiner	(96)	Carcinoma and sarcoma of gall-bladder.
Lindemann	(101)	Carcinoma sarcomatodes of stomach.
"		Carcinoma sarcomatodes of uterus.
Lippmann	(102)	Carcinoma sarcomatodes of ovary.
Loeb	(103)	Carcinoma and sarcoma of thyroid (white rat).
Maier	(106)	Carcinoma and sarcoma of tibia.
Meyer	(111)	Carcinoma and sarcoma of uterus.
Michelson	(113)	Carcinoma sarcomatodes of pancreas.
Nebesky	(116)	Carcinoma and sarcoma of uterus.
Niebergall	(118)	Carcinoma, sarcoma and polyp of uterus.
Opitz	(122)	Carcinoma sarcomatodes of uterus.
Orth	(124)	Carcinoma and sarcoma of breast.
Quekenstedt	(134)	Carcinoma sarcomatodes of stomach.
Rabl		
Rückhardt	(135)	Carcinoma and sarcoma of ovary.
Rezek	(141)	Glioma of substantia nigra, sarcoma of right temporal lobe.
Ritter	(144)	Carcinoma and sarcoma of uterus.
Rosenstein	(146)	Carcinoma sarcomatodes of uterus.
Rothacker	(147)	Carcinoma and sarcoma of ovary.
Saltykow	(149)	Carcinoma and spindle-celled sarcoma of thyroid.
"	(150)	Carcinoma sarcomatodes of uterus.
"	(150)	Carcinoma and sarcoma of liver.
"	(150)	Carcinoma and sarcoma of lung.
Shaller	(151)	Adenocarcinoma and giant-celled sarcoma of uterus.
Schlagenhauser	(156)	Carcinoma and giant-celled sarcoma of breast.
Schmorl	(158)	Carcinoma and sarcoma of thyroid.
Schone	(159)	Carcinoma and sarcoma of thyroid (dog).
Stein	(166)	Carcinoma sarcomatodes of uterus.
Stromeyer	(167)	Cholesteatoma and sarcoma of temporal lobe of brain.

Takano	(169)	Carcinoma sarcomatodes of breast.
Taylor	(171)	Carcinoma and sarcoma of thyroid.
"		Adenocarcinoma and sarcoma of uterus.
"		Adenocarcinoma and sarcoma of body of uterus, epithelioma of cervix.
Wehmer	(188)	Carcinoma and sarcoma of breast.
Wells	(190)	Alveolar carcinoma, angiosarcoma of thyroid (dog).

## DIFFERENT TUMORS IN SAME SYSTEM OF ORGANS

Beadles	(10)	Carcinoma of uterus, sarcoma of breast.
Czerny	(35)	Carcinoma of one breast, sarcoma of the other breast.
Haberer	(61)	Carcinoma of tongue, spindle-celled sarcoma of epiglottis.
Langdon	(97)	Fibrocystoma of pons, fibrosarcoma of dura.
Scheel	(152)	Carcinoma of breast, spindle-celled sarcoma of ovary.
Schiller	(155)	Carcinoma of tongue, sarcoma of epiglottis.
Thierfelder	(175)	Squamous-celled carcinoma of esophagus, spindle-celled sarcoma of stomach.
Vander Veer	(180)	Carcinoma of breast, multicellular ovarian cyst.
Walter	(185)	Carcinoma of esophagus, spindle-celled sarcoma of stomach.

## DIFFERENT TYPES OF TUMORS IN VARIOUS ORGANS

Auerbach	(6)	Carcinoma of gall-bladder, spindle-celled sarcoma of leg.
Bartel	(8)	Neuromata at base of brain, endothelioma of dura mater.
Bartlett	(9)	Carcinoma of thyroid, adrenal mesothelioma, congenital cystic kidneys, hemangioma of liver (dog).
"		Adenocarcinoma of thyroid, mixed tumor of breast, adenoma of adrenal (dog).
Beadles	(10)	Epithelioma of pharynx, malignant adenoma of kidney.
"		Carcinoma of breast, sarcoma of skin of groin.
Beck	(12)	Carcinoma of gall-bladder, spindle-celled sarcoma of thyroid.
Bevacque	(19)	Peritheliomata of bone, lymphosarcoma of lymph glands.
Blackburn	(20)	Sarcoma of dura, carcinoma of stomach, round-celled of testicle.
Borst	(25)	Carcinoma of thyroid, fibroma of kidney, fibroma of uterus, papilloma of skin.
Cathcart	(28)	Melanotic sarcoma, scirrhous carcinoma.
Chambers	(29)	Carcinoma of both breasts, sarcoma of uterus, sarcoma of skin.
Coenen	(32)	Sarcoma of fascia, myoma of esophagus, hypophysis tumor.
Foster	(47)	Hypernephroma of kidney, scirrhous carcinoma of stomach.
"		Hypernephroma of kidney, carcinoma of stomach.
Fraugenheim	(50)	Endothelioma of dura, carcinoma of ovary.
Grawitz	(58)	Carcinoma of small intestine, sarcoma of broad ligament, myoma of uterus.
Griffin	(59)	Carcinoma of esophagus, sarcoma of skin.
Grunfeld	(60)	Colloid carcinoma of stomach, angioendothelioma of stomach.
Hanot	(63)	Carcinoma of liver, sarcoma of uterus.
Hansemann	(64)	Glioma cerebri, myxoma of stomach, sarcoma of liver.



Herrxheimer (69) Carcinoma of stomach, sarcoma of brain, myoma of uterus, polyp of stomach.

Krakiewicz (88) Squamous-celled carcinoma of esophagus, lymphosarcoma of mediastinum.

Kretz (89) Carcinoma of esophagus, endothelioma of dura.

Landau (95) Osteoma of jaw, adenocarcinoma of intestine and rectum, fibrosarcoma of breast.

van Leuwen (99) Basal-celled carcinoma of skin, mixed tumor of parotid.

Lewis (100) Angioma of liver, angioma of kidney, adenoma of liver, adenoma of adrenal, polyp of uterus, myoma of uterus, malignant myoma of broad ligament, fibroma of ovary, pigmented navi.

Mann (108) Epithelioma of penis, endothelioma of dura.

Markus (109) Carcinoma of liver and gall-bladder, melanotic sarcoma of ovaries.

Nehrkorn (117) Carcinoma of uterus, melanotic sarcoma of rectum.

Nothdurft (119) Carcinoma of both kidneys, hemangioma of breast.

Phillipson (129) Carcinoma of gall-bladder, sarcoma of skin.

Scheven (154) Carcinoma of stomach, mixed tumor of kidney, psammoma of left striate body.

Schmincke (157) Carcinoma of gall-bladder, sarcoma of uterus.

Simon (162) Carcinoma of liver, melanotic sarcoma of eye.

Sliwinsky (164) Carcinoma of breast, carcinoma of stomach, papillary adenoma of kidney, lipoma of mesentery, endothelioma of dura, multiple adenomata of thyroid, carcinoma of liver.

Taylor (171) Carcinoma of thyroid, sarcoma of mediastinum.

" Carcinoma of liver, melanotic sarcoma of choroid.

Thal-messinger (172) Cystoma of ovary, sarcoma of peritoneum.

" Carcinoma of penis, lymphosarcoma of inguinal lymph gland.

" Adenoma of breast, osteosarcoma of tibia.

" Carcinoma of right ear and cheek, large round-celled sarcoma of neck.

Ugdalena (179) Adenoma of hypophysis, carcinoma of uterus.

Vander Veer (180) Carcinoma of breast, sarcoma of dura.

Walter (184) Carcinoma of pancreas, sarcoma of liver.

" (185) Carcinoma of stomach, psammoma of brain, liposarcoma of kidney.

Wehmer (188) Carcinoma of uterus, adenocarcinoma of ovary, sarcoma of peritoneal cavity.

Wooley (195) Gliosarcoma of brain, endothelioma of pleura, endothelioma of Glisson's capsule.

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## IDIOPATHIC BACILLUS AEROGENES CAPSULATUS INFECTION

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Since Welch and Nuttall<sup>1</sup> published a description of this organism, in 1892, many reports of infection with it have appeared in the literature. Although most of the cases recorded have been instances where crushing or severe mechanical injury was followed by a phlegmonous and usually fatal inflammation, for which the bacillus in question was adjudged to be responsible, some of the patients have had no such predisposing injury. The puerperal cases, of course, may be said to follow the severe traumatism not uncommonly associated with difficult labor, but such cases of this infection as that reported by Gwyn<sup>2</sup>, which presented at first clinically as chorea, cannot be attributed to traumatism, at least to external traumatism. In this case, 13 days before death, a blood culture showed the presence of the *B. aerogenes capsulatus* alone. Later, endocarditis was discovered and, in addition to the bacillus in question, streptococci were found in another blood culture.

As the organism is a recognized common inhabitant of the intestinal tract and of distinct pathogenic abilities, it would be expected that lesions of the abdominal organs, due to various pathological conditions such as tumor, obstruction, ulceration, acute indigestion etc., and the inevitable traumatism

of abdominal surgery, would, not infrequently, be followed by inflammations directly caused by this bacillus. As the predisposing conditions in such cases are usually obscure they may properly be classed as idiopathic infections.

A cursory glance at recent literature, however, yields very little to prove such a supposition, perhaps because bacteriological investigations have been so seldom undertaken: Libman<sup>3</sup> reported a case of gall-bladder infection due to this organism. Baugher<sup>4</sup> reported three cases—one in which suppurative perforation of the gall-bladder was apparently caused by this organism; another in which it was found in a fistula which followed an operation for cholecystitis and which led to perforation of the stomach; and a third in which it was the infectious agent in a chronic fistula leading to the gall-bladder region, and in an acute right-side empyema, which followed operations necessitated by an appendiceal abscess.

Several authorities<sup>5</sup> have reported certain small epidemics and individual cases of severe diarrhoea in which it seemed reasonable to conclude that the *B. aerogenes capsulatus* was the causative factor. In this connection Hewes and Kendall made the interesting observation that diarrhoeas due to this organism were aggravated by such diet (carbohydrates, especially sugar)

as had been demonstrated to be beneficial in cases where dysentery bacilli were operating; while regimens consisting principally of proteins gave the best results in such cases as might be blamed upon the *B. aerogenes capsulatus*.

A case of primary osteomyelitis at the sacro-iliac joint was reported by Cone<sup>4</sup>. The patient died from the generalizing of the infection and the autopsy disclosed post-mortem gaseous accumulations in the spleen, subcutaneous and other tissues. *B. aerogenes capsulatus* was found in necrotic bone around the primary focus.

A case of long continued ear discharge, followed by acute mastoiditis and lateral sinus thrombosis was reported by Shortlidge.<sup>7</sup> The patient, a man, died.

Cramp<sup>8</sup>, in summarizing reports of 187 cases of infection with this bacillus said that 76 resulted from compound fractures; 41 from lacerated wounds; 15 from gun-shot injuries; 3 from bites by animals; 2 from gorings by cattle; 21 were post-operative; 8 followed subcutaneous injections; 6 occurred in gynecological or obstetrical cases; and 6 were non-traumatic and, therefore, of similar origin to the cases called idiopathic in this article. The remaining cases of the 187 were not classified.

Besson<sup>9</sup> says: "The bacillus perfringens (*B. aerogenes capsulatus*) is exceedingly widespread. Achalmé found it in the blood of persons suffering from rheumatism and in the myocardium of two individuals who had died of acute articular rheumatism; Veillon and Zuber in gangrenous suppurations (appendicitis, etc.); Guyon, Albarran, Jungano, in urinary abscesses; Fraenkel in an inflammatory swelling; Guillemot in a case of gaseous gangrene; Jungano in cases of chronic urethritis; Chaillous and Benedetti in ocular infections. It is a normal inhabitant of the alimentary canal of man and many of the lower animals, and it possibly plays a part in the etiology of certain forms of diarrhoea (Tissier, Metchnikoff). It is also present in bodies undergoing decomposition."

In connection with inflammatory processes of the gall-bladder and liver I recently had occasion to do some bacteriological and pathological work which disclosed two interesting cases of infection by *B. aerogenes capsulatus*.

The first patient had been under the care of Dr. Earle H. Mayne of this city, who has very kindly supplied me with clinical data sufficient to give a short account of the case.

Mrs. B., a housewife of 52 years of age, in prosperous circumstances, weight about 160 lbs., previously in good health and with a negative disease history, after having been ailing and, more or less, confined to the house for about three months, called in Dr. Mayne, who found her suffering from a remittent fever, reaching from 100° to 104° F. in the afternoons and subsiding slightly in the mornings. There were no other symptoms except such lassitude and anorexia as would naturally accompany any toxæmia producing such elevation of temperature. Upon physical examination, Dr. Mayne found that the patient's liver reached a point half-way between the lower margin of the ribs and the

umbilicus. At his request I made laboratory examinations which gave the following findings:

#### Blood—

Erythrocytes: 4,400,400 (slight poikilocytosis, otherwise the cells were normal).

Leucocytes: 32,400 (neutrophile, 69 per cent; eosinophile, 7.2 per cent; lymphocytes, 17.8 per cent; large mononuclears, 6 per cent.

No malaria plasmodia were present, and the Widal and Wassermann tests were negative. The feces showed nothing beyond the usual miscellaneous assortment of bacteria, a good deal of mucus, and epithelia from the large intestine.

Blood cultures, taken two weeks before the date of the above tests, were negative; but those taken concomitantly gave, after 48 hours' incubation, a pure growth of what subsequently proved to be the *B. aerogenes capsulatus*.

The patient refused an exploratory laparotomy and Dr. Mayne then proceeded to immunize her son with a vaccine which I made from the organism isolated. After three doses had been given the young man, 500 c. c. of his blood were transfused into his mother; again three injections of vaccine into the donor, a transfusion of 800 c. c. to the patient; and, finally, a third series of three doses of vaccine, and a transfusion of 1000 c. c. of blood. No noticeable effect was produced, and nothing else that was done for the patient helped her in any way.

During the next three months the patient gradually grew worse, her liver finally reaching to Poupart's ligament. For the last 10 days of this period she was delirious, dying, evidently from toxæmia, after an illness of six months.

An autopsy was obtained by Dr. Raymond Clark, who had cared for the patient during an absence from town of Dr. Mayne. Dr. Clark informs me that the post-mortem disclosed a generalized carcinoma of the liver, which seemed, possibly, to have arisen in the gall-bladder, which was extensively diseased. No bacteriological examination was made at this time.

Since the high temperature prevailing during the six months illness necessitates an explanation other than the presence of

Number Cases	Nature of Case	Outcome		Positive Culture	Reported by
		Deaths	Recoveries		
1	Puerperal.	1	....	Few days before death.	Young & Rickard, Boston M. & S. J., 1906, C. L., p. 391.
1	Chorea, endocarditis.	1	....	13 days before death.	Gwyn, Bull. J. Hopkins Hosp., 1899, X, p. 134.
1	Severe injury.	4	....	Few hours before death.	Hewitt, J. A. M. A., Apr. 1, 1911, p. 906.
1	Severe injury.	1	....	3 hours before death.	Colt, Bull. J. Hopkins Hosp., 1902, VIII, p. 354.
1	Severe injury.	1	....	1 day before death.	Baughor, J. A. M. A., Apr. 11, 1914, p. 1153.
1	Cholecystitis.	....	1	....	Baughor, J. A. M. A., Apr. 11, 1914, p. 1153.
1	After operation for cholecystitis.	....	1	....	Baughor, J. A. M. A., Apr. 11, 1914, p. 1153.
1	After operation for appendicitis.	....	1	....	Baughor, J. A. M. A., Apr. 11, 1914, p. 1153.
1	Carcinoma of liver.	1	....	3 months before death.	Prescott communication.

the neoplasm, and as the positive blood cultures and leucocytosis demonstrated the presence of an infection with *B. aerogenes capsulatus* and a systemic reaction thereto, I think it justifiable to conclude that the neoplasm afforded a gateway by which this common saprophyte was enabled to maintain

\* "Practical Bacteriology, Microbiology and Serum Therapy" (English edition). Longmans.

an infectious process extending probably from the gall-bladder into the liver, whence toxins\* and organisms reached the general circulation with the results manifested during life.

It is, of course, possible that antecedent injury of the gall-bladder by the activities of the organism in question furnished that continued irritation thought to be so important in determining the site of a neoplasm.

An interesting feature of this case was the positive blood culture obtained three months before death. In the literature

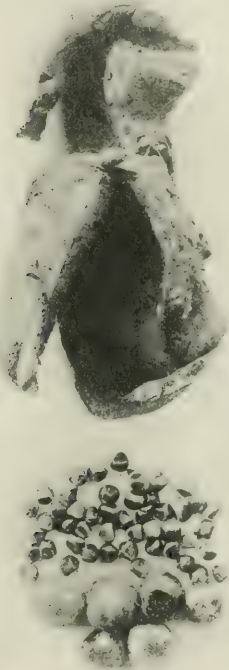


FIG. 1.—Gall-bladder and gall-stones from case of chronic cholecystitis due to *B. aerogenes capsulatus*.

positive blood culture cases (showing the *B. aerogenes capsulatus*) are so rare as to justify a résumé of those found, which are given in the table opposite.

A somewhat similar case was one recently operated upon by Dr. G. de Yoanna of this city, in which he removed the gall-bladder shown in the accompanying illustration. The patient, Mrs. C., was a married woman, 30 years of age, who had complained of repeated attacks of indigestion. When

Dr. de Yoanna examined her abdomen he readily detected the projecting mass formed by the diseased gall-bladder. It was not tender and the patient was afebrile, but, since the finding was so markedly pathological, he determined to operate. The diseased structure, although extensively adherent to adjacent organs, was removed but, unfortunately, the patient died two days later.

Upon examination of the gall-bladder I could find no lesions other than excessive hypertrophy of its muscular and fibrous elements (its wall was over three-quarters of an inch thick) and catarrhal inflammation of the mucosa. The gall-bladder contained, besides the gall-stones shown in the photograph, nearly clear serous fluid in which I found many bacilli, most of which were in the degenerated state connected with spore formation. Cultures from this fluid gave a pure growth of the *B. aerogenes capsulatus*. The gall-stones were of cholesterolin, and from the centers of two of them I grew a culture of the same organism, this indicating that it probably was concerned in the formation of the concretions.

#### IDENTIFICATION OF ORGANISMS

In the case of the blood culture from Mrs. B., the first organisms that were obtained were from the bottom of a narrow tube of about 10 c. c. of bouillon, to which had been added 0.5 c. c. of the patient's blood. These bacilli were observed after 48 hours' incubation, at 37.5° C.\* Replants in bouillon, after two to three generations, diffusely clouded the medium. The organisms were non-motile. In old cultures many of the bacilli showed the non-stain-taking oval form associated with spore formation. Cultures (replants from bouillon) in neutral milk, within 24 to 48 hours, coagulated the medium with acid reaction and rancid odor. Replants in dextrose-agar developed bubbles of gas. Young organisms were always gram-positive.

A guinea-pig, intravenously inoculated with 0.5 c. c. of a culture in bouillon-serum, was killed a few minutes later, incubated for 24 hours and autopsied. Gas was found in the heart, the larger veins, and in the liver. Many large capsulated bacilli were evident in smears made from the blood.

In the second case (Mrs. C.) a culture, from the nucleus of a gall-stone, in bouillon-serum, was replanted in milk, which it coagulated, as above, giving an odor of butyric acid.

A bouillon-serum culture (0.5 c. c.) was injected into a guinea-pig, which was killed five minutes later, incubated for 24 hours and autopsied. Bubbles of gas, and capsulated bacilli were found as in the case first described.

#### RECENT BACTERIOLOGICAL WORK

Work of a great deal of interest has been published during the past year in connection with the conditions affecting the growth of this bacillus. Wright\* conducted extensive experiments by which he showed that it would grow most prolifically

\* Bull and Pritchett (J. Med., 1917, XXVI, pp. 119) recently demonstrated that this bacillus could produce a toxin which was hæmolytic and able to disintegrate tissue elements generally.

\* Besson (p. 570) quotes Rosenthal to the effect that the latter had grown the bacillus under aerobic conditions. Baugher (quoted before) did not employ anaerobic conditions in growing his blood cultures.



in a tube of bouillon to which a piece of potato (or various other substances) had been added, under aerobic conditions. Since he obtained similar results by adding to the bouillon, instead of potato, pledgets of cotton or of asbestos wool, platinum black, a rusty nail, a capillary glass tube filled with a minute quantity of a suspension of the organisms, he concluded that the common factor involved was of a mechanical nature. He says: "And that mechanical factor would appear to be the providing of some hole or cranny to serve as a nidus in which the microbe can get a start by concentrating its chemical effort at first upon a fractional portion of the provided culture medium."

Continuing his experiments he determined that trypticized serum was considerably more favorable to the growth of the organism than normal serum, and declared that what he calls the "antitryptic power of the blood" stood in the way of the growth of this organism, as well as of others, by inhibiting the digestive processes by which microorganisms obtain their food. Of course, it seems that this so-called antitryptic power may represent nothing more than the minimal power (amount) of bacterial enzyme that is required to make a salient (militarily speaking) into the normal serum or blood elements, or the resistance to bacterial digestion (the chemical inertia) displayed by the smallest units of the said serum upon which the bacterial forces can be brought to bear.

Wright, commenting upon the difficulty met with in starting growth of cultures of the *B. aerogenes capsulatus* in serum and the avalanche-like progress made when once such a start had been effected, compared this to the way in which wound infections with this organism often become rapidly progressive.

Considering the acidity developed in serum by the growth of this bacillus he experimented with serum of which the natural alkalinity had been neutralized by the addition of sulphuric acid, and found that the addition of the acid converted an unfavorable into a most favorable medium. The lesson of this experiment was applied clinically, and Wright reports that the administration of alkalis to patients suffering from serious wound infections with the bacillus in question "gave markedly favorable results only in two cases out of the six" experimented upon.

In this connection it occurs to the writer that the reason the addition of acid, especially a mineral acid, to an albuminous fluid such as blood serum, aids in the growth of a peptonizing microorganism therein, is that here the same forces operate as in the human stomach where peptic digestion is so greatly dependent upon the presence of acid.

Taylor and Austin<sup>11</sup> recently announced that "Dakin's hypochlorite and chloramine-T solutions will protect pigeons against multiple fatal doses of the toxin of *B. welchii* when the antiseptic and the toxin are mixed *in vitro* and allowed to stand in contact for five minutes before injection. The detoxicating action of the solutions is demonstrable also in the presence of serum. Phenol solution, 0.25 per cent, has no such action."

They quote Dakin to the effect that this action of the chlorinated antiseptics is to be attributed chiefly to their affinity for the amino group of the protein molecule. It seems to me

that a simpler and more probable explanation would be that these solutions acted in an antacid capacity upon a toxin which Wright proved to be more active in an acid or at least a neutral medium. The failure of the phenol to modify the effect of the toxins may be explained along the same lines, as it would tend to increase acidity, certainly not to reduce it.

Wolf, McGill and Harris,<sup>12</sup> after experimenting with this same organism along the lines pursued by Wright, announced that "with a properly prepared culture medium *B. welchii* will grow freely in open, narrow tubes. The addition of any solid matter is not necessary to produce this apparently aerobic growth. No segregation of organisms is necessary, for the bacillus grows vigorously when nitrogen containing 1 per cent of oxygen is bubbled continuously through the tubes, but the organism is very sensitive to, and its growth is inhibited by, higher proportions of oxygen. For this reason the so-called aerobic growth is best obtained in narrow tubes of freshly sterilized fluid from which the air has been partly expelled by the heat of sterilization."

In regard to the layer of oil that some have thought necessary and so frequently employ in cultivating certain organisms, a statement by these authors is most interesting and undoubtedly entirely true:

"In connection with the conditions which are usually associated with anaerobic technique it would appear that bacteriologists have been deluded for a long time into thinking that by covering a culture medium with a layer of paraffin or lanoline the aqueous layer is protected from the gases of the atmosphere. Vernon, as quoted by Bayliss in his "Principles of General Physiology," found that oxygen was 4.5 times more soluble in fats and oils than in water. Bayliss directs attention to the futility of attempting to protect aqueous solutions from the gases of the atmosphere with layers of oil, as is done in Hesse's method. The anaerobic conditions desired can be just as well obtained by employing high, narrow tubes of freshly sterilized media.

"We have a certain number of experiments which confirm Bayliss's statement in every particular. Sloped tubes covered with paraffin do not grow the bacillus any better than do similar tubes unprotected by the fatty layer. If the paraffin layer is of any real value, it probably plays its part in diminishing convection currents in the aqueous layer."

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## ABSTRACT OF PAPER

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin

Prepared by the Authors

## OBSERVATIONS UPON THE CALCIUM CONTENT OF THE BLOOD IN INFANTILE TETANY AND UPON THE EFFECT OF TREATMENT WITH CALCIUM

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The diagnosis of tetany at the present day from clinical symptoms and by means of the accessory diagnostic signs may be made with sufficient accuracy; it is another matter to determine what it is that brings about this strange hyperexcitability of the nervous system to insults and stimuli of all kinds. There have been many hypotheses suggested. None has been as yet entirely convincing. It has been vigorously insisted that tetany is only a symptom of rickets. It is quite true that rickets is usually to be found associated with tetany and that tetany is most common during the winter and spring months when active rickets is also most frequently seen. The chief objections to this hypothesis are that tetany is found at times when no rickets is discoverable and that very many children with the most extreme evidences of rickets never manifest any evidences of tetany.

Tetany has been referred to an improper diet, to an absence of breast milk or to an excessive quantity of cow's milk. That no particular food can be held solely responsible is shown by the fact that tetany may be seen after almost any form of diet.

Tetany has also been referred to the absence of an essential substance or "vitamine" in the diet. In support of this view may be mentioned the preponderance of tetany among the artificially fed and the considerable improvement brought about by codliver oil. Against this view is the fact that many cases of tetany are to be seen when the diet of the infants has been composed wholly or in part of cow's milk which has not been heated and hence still contains the vitamins.

Noël Paton and his collaborators have recently made an extensive study of tetany in animals and in human beings. They believe that the tetany of animals deprived of their parathyroid glands and the idiopathic tetany of infants are similar as regards their characters and metabolism, and that both are due to some error in metabolism whereby an intoxication by guanidin and methyl guanidin takes place. Until the chemical studies upon which these conclusions are based can be repeated and confirmed, it would be premature to venture a definite opinion regarding them. There are certain facts, however, that merit consideration. In the first place, enough studies have been made to show that parathyroid lesions in infantile tetany are the exception and not the rule. It should also be stated that parathyroid lesions as severe as have been found after tetany may occur in patients who, during life, have shown absolutely no evidences of tetany,

electrical or otherwise. Another possible ground for criticism of Paton's conclusions is found in the small number of observations upon children and in the unsatisfactory ages of the children used for control. Finally, granting that the analytical method used by Paton determines guanidin and methyl guanidin alone, no proof has been brought forward that the substances have accumulated in the blood of children.

Some objections to the view that parathyroid disease is the cause of infantile tetany have been mentioned. That there are many points of similarity between the tetany of parathyroidectomized dogs and human tetany is true. The symptoms are much alike as are also the electrical reactions. The changes that MacCallum and Voegtlin found in the calcium of the blood are, as will be seen later, strikingly like those that we have found in the tetany of infants. But the experiments of Binger show that typical tetany may be produced in dogs when the parathyroids are left entirely undisturbed.

More attention has probably been paid to calcium as a factor in the production of infantile tetany than to any other chemical substance. The close connection between rickets and tetany, in the former of which there is a known error of calcium metabolism, has been sufficient to suggest to many a somewhat similar disturbance of calcium metabolism in tetany. A great stimulus to the study of the relation of calcium to tetany was given by the observation of Sabbatani and other Italian investigators, that a solution of calcium applied to the brain diminished its irritability to electrical stimulation, but substances that caused a precipitation of calcium such as oxalates or citrates brought about an increased irritability.

The favorable therapeutic influence of calcium upon tetany gives weight to the view that a deficiency of calcium may play a part in the production of tetany. Studies upon the calcium metabolism of infants with tetany have been made by v. Cylbulski and Schabad. The former found a very slight calcium retention during active tetany and a greatly increased retention during convalescence. Schabad's results were similar. He came to the conclusion that there was absolutely no difference to be determined between the metabolism of uncomplicated rickets and of rickets complicated by tetany and stated that the information to be desired could be obtained only by analyses of the blood. He, however, made none.

The attempt has been made by Neurath, Cattaneo, and Longo to determine the calcium in the blood. Neurath used Wright's method, which is supposed to show differences in the amount of free calcium ions. It gives relative but not absolute figures. Neurath examined the blood of 15 infants with various manifestations of tetany of more or less severity. He found in general a reduction of the calcium. No determinations were made upon patients with rickets alone.

Cattaneo and Longo have made gravimetric determinations of the calcium in the blood of a few normal children and of

a few with tetany. Their results were at variance and Longo concluded that it was impossible to establish any relationship between the amount of calcium in the blood and any manifestation of tetany.

The studies upon parathyroid tetany in animals are of great interest on account of the influence of parathyroidectomy upon the calcium of the blood. MacCallum and Voegtlin and MacCallum and Vogel have shown that after parathyroidectomy tetany appeared when the calcium of the blood was diminished about one-half and that the symptoms of tetany could be promptly, though only temporarily, relieved by the intravenous administration of calcium salts.

A year ago we showed that in the acidosis of nephritis there is a great accumulation of inorganic phosphates in the blood serum, and that when the phosphates are increased there is a reduction of the calcium, sometimes to a very low point. On the basis of these findings Binger has recently published interesting observations upon the effect of the intravenous administration of phosphate solutions to dogs. When sodium phosphate in sufficient quantity and at the right reaction is injected, definite tetany results with a marked decrease in the calcium of the serum. If the solution injected has a hydrogen-ion concentration greater than  $10^{-6}$  no tetany results even though the calcium drop occurs.

We have studied the relationship of calcium and infantile tetany during the last 2½ years. It is apparent that merely from the determination of the intake and excretion of calcium, little can be learned. It is of prime importance to determine the quantity of calcium circulating in the blood. With the usual methods of analysis this has been impossible unless 50 or 100 c. c. were withdrawn, with double the amount if duplicate determinations were made—an impossible procedure with living infants. It was therefore necessary to develop an accurate method that would allow duplicate determinations to be made with a small amount of blood. This we have done. The method is sufficiently exact to determine the calcium in 2 c. c. of serum with an error of not more than 5 per cent.

We determined first the calcium in the serum of normal persons. The amounts found are given in Table I.

TABLE I.—NORMAL

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

Placental	11.3	15 months	11.0
Placental	11.0	Adult	11.2
Placental	10.8	Adult	11.3
Placental	10.7	Adult	9.2
6 weeks	11.0	Adult	10.0
3 months	10.0	Adult	10.3
3 months	11.0	Adult	11.0
5 months	10.8	Adult	9.8

It will be seen from the table that the quantity of calcium in placental serum and in the serum of normal patients is singularly constant. In almost all instances, no matter what

the age, and in all instances with infants it was above 10 mg. and it is seldom more than 11 mg.

On account of the frequent association of rickets with tetany it was necessary to determine if any changes in the calcium of the serum results from rickets alone. We have therefore studied a considerable number of cases of rickets.

TABLE II.—RICKETS

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

No.	Child	Race	Age	Type of Rickets	Calcium
1	A. T.	Colored	4 months	Active	10.9
2	R. W.	Colored	4 months	Active	9.0
3	C. J.	Colored	4 months	Active	10.5
4	L. D.	Colored	4 months	Active	7.9
5	D. S.	Colored	4 months	Active	9.0
6	G. D.	Colored	4 months	Active	8.0
7	E. F.	Colored	4 months	Active	9.0
8	H. L.	Colored	4 months	Active	8.3
9	E. B.	Colored	4 months	Active	9.3
10	B. S.	Colored	6 months	Mild	10.9
11	M. S.	White	6 months	Mild	10.7
12	C. F.	White	6½ months	Moderate	8.6-9.0
13	M. S.	White	8 months	Mild	10.9
14	T. L.	White	8 months	Moderate	9.0
15	L. W.	White	8 months	Marked	10.5
16	F. F.	White	9 months	Marked	9.0
17	E. V.	White	10 months	Mild	8.0
18	R. Q.	Colored	12 months	Mild	9.8
19	R. Q.	Colored	14 months	Mild	8.8
20	J. M.	White	20 months	Marked	10.0
21	S. J.	Colored	23 months	Very severe	9.3

Average .... 9.4

An examination of the figures in Table II shows that in more than a third of the cases the figures fall within the normal limits, and this even when the disease was presumably active (in the fourth and sixth months). In 9 cases there was a slight reduction, so that there were found between 9 and 10 mg. of calcium per 100 c. c. In 5 cases the calcium content was from 7.9 to 8.8 mg. The lowest amount that we have found in apparently uncomplicated rickets was 7.9 mg. We may say, then, that with rickets there is no great reduction in the calcium, that while the calcium may be reduced as much as 2 mg. per 100 c. c. (20 per cent) the considerable majority show a reduction of 1 mg. (10 per cent) or less, and that with cases of apparently active rickets there may be no reduction whatever. The calcium reduction does not seem to be obligative.

In choosing cases of tetany for study we have taken those regarding the diagnosis of which there could be no doubt whatever. All of the children had had or were having convulsions, with all there was a cathodal opening contraction with a current less than 5 milliampères, a number had spasm of the glottis, and with many Trousseau's sign or a marked facial phenomenon, or both, were demonstrated.

Table III gives in tabular form the calcium in the serum, during active symptoms, with the 18 cases of idiopathic tetany which we have studied.



TABLE III.—ACTIVE TETANY

MILLIGRAMS OF CALCIUM PER 100 C. C. OF SERUM

Case 1	6.0	Case 11	6.0
Case 2	5.7	Case 12	6.5
Case 3	5.5	Case 12	6.15
Case 4	5.0	Case 13	6.3
Case 5	5.0		6.5
Case 6	5.8	Case 14	6.8
Case 7	3.5	Case 15	6.0
Case 8	5.0	Case 16	7.3
	6.3	Case 17	5.0
	5.0	Case 18	4.6
	4.5		
Case 9	4.7		
Case 10	5.8	Average	5.6

It will be noticed that the calcium was very greatly reduced in all instances, and with one exception was 7.0 mg. or less per 100 c. c., a reduction, roughly, in the neighborhood of 40 per cent. It will also be noticed that the calcium was, in all instances, less than we have ever found with rickets and so much lower that, with one or two exceptions, there could be no danger of confusing even the highest determinations with the lowest which we obtained in rickets. From the regularity of our findings it appears that convulsions may be expected when the calcium content of the serum becomes less than 7.0 mg. per 100 c. c., or, to put it in another way, when there are convulsions and other symptoms due to tetany, the calcium of the serum is 7.0 mg., or less, per 100 c. c. The amount of calcium in the serum that we found in idiopathic tetany is strikingly close to that which was found by MacCallum and Vogel in the serum of dogs after parathyroidectomy. They determined the calcium in whole blood. Considering the calcium of serum twice that in an equivalent amount of whole blood, their results may be reckoned as 3.1, 6.4, 4.5, and 7.8 mg. per 100 c. c.

The results obtained by Binger are also strikingly similar. He found that dogs, after injection with a sodium phosphate solution of the proper hydrogen-ion concentration, developed tetany when the calcium in the serum was 5.6, 6.1, 5.5, and 5.3 mg., respectively, and that tetany did not develop when the calcium of the serum was reduced by the same measures to 7.8, 7.7 and 7.7 mg., respectively. We have also found in studying the serum of two dogs subjected to parathyroidectomy that the symptoms of tetany developed when the calcium was reduced to about 7.0 mg. Thus, one dog, before operation, had 10.8 mg. of calcium per 100 c. c. of serum; after 48 hours, a short time before the onset of tetany, 7.3 mg., and the second had, before operation, 10.0; after 24 hours, 8.9; and after 6 days and with the onset of tetany, 6.8 mg., per 100 c. c. of serum.

The constancy in the diminution of the calcium of the serum in tetany affords some means of differentiating tetany from other convulsive disorders in infancy. We have studied other cases of convulsions, manifestly not due to tetany, and have found the following:

TABLE IV.—CASES OF CONVULSIONS NOT DUE TO TETANY

Patient	Age	Diagnosis	Mg. of Calcium per 100 c. c. of Serum
S. S.	4 months	Mental deficiency	10.1
C. deF.	1 year	Petit mal	11.0
D. N.	2½ years	Epilepsy	10.2
J. B.	5 years	Epilepsy	8.9
R. G.	7 months	Convulsions of unexplained origin	9.6
M. S.	6 months	Convulsions of unexplained origin	10.7
H. B.	7 months	Convulsions of unexplained origin	9.2

In the light of these results is it possible to refer tetany to a diminution of calcium in the blood? Perhaps the strongest evidence, in addition to the great parallelism which we have found between the symptoms and the low calcium content of the serum, is the results obtained by Binger after the injection of orthophosphates. When the calcium was reduced to a figure closely corresponding to what we found with active tetany, the characteristic symptoms of tetany in the dog appeared, and this when the parathyroids were entirely untouched. The prompt improvement in infantile tetany after calcium medication, as will be shown, and the absence of symptoms when the calcium in the blood remains above 7.5 mg., is also strong evidence as to the part that calcium plays in the production and dissipation of symptoms.

It seems sufficiently plain that the diminution in the calcium of the serum is a constant phenomenon in infantile tetany. What is it that brings about this diminution? The question arises: Is there an accumulation of inorganic phosphates of the serum in tetany sufficient to account for the reduction of the calcium? This question can be answered at once in the negative. We have determined the inorganic phosphorus, in active tetany, the calcium being low, and have not found an amount of phosphorus in the serum significantly above the normal limits, which are from 1 to 3.5 mg. per 100 c. c. of serum. We have found in tetany 1.0, 3.0, 4.0 and 2.7 in different cases.

Wilson, Stearns, and Thurlow showed that in dogs at certain stages of tetany induced by parathyroidectomy, there was an increased alkalinity of the blood called by them "alkalosis." This disappeared after the onset of convulsions. We have made determinations of the hydrogen-ion concentration of the serum of infants with tetany by the dialysis indicator method but have not found an "alkalosis." That tetany may, however, at times result from an alteration in the reaction of the blood we have had opportunity to observe. After the therapeutic administration of bicarbonate of soda for acidosis, it is not unusual to see the development of characteristic symptoms of tetany. Thus, we have seen typical carpopedal spasm when bicarbonate of soda has been injected intravenously for the acidosis of diarrhoea. The onset of symptoms of tetany following the administration of soda and their prompt cessation when the soda was stopped, with the changes in the calcium content of the serum and the electrical reactions, indicate that soda is capable of producing these symptoms.

It is apparent that the symptoms of tetany and the lowering of the calcium content of the serum may be produced in a variety of ways, but we have not been able to show that any of these means is operative in uncomplicated infantile tetany.

Calcium and magnesium, both constituents of the serum, are chemically closely related, and from the physiological standpoint it has been shown that their action is frequently similar though at times it may be distinctly antagonistic. For this reason it appeared advisable to determine also the magnesium in the serum. It was necessary to devise a special method for this as the amount in the serum is so small that gravimetric determinations are out of the question. This we have done. The method is sufficiently accurate to determine the magnesium in 2 c. c. of serum with an error of not more than 5 per cent. The determination may be made with the same sample of serum in which the calcium is determined. It has been found that the amount of magnesium in the serum shows but little variation. Not only is this true during health but it is also true in disease. We have not found less than 1.75 mg. or more than 4.0 mg. of magnesium per 100 c. c. of serum. The slight variations in the magnesium seem to bear no relationship to the alterations in the calcium. It is, therefore, possible to say that magnesium plays no determining rôle in the production of the symptoms of tetany.

Our results are sufficiently numerous to allow certain conclusions to be drawn regarding the specificity of the electrical reactions of tetany. In all instances when the C. O. C. or C. C. T. occurred with a current of less than 5 milliamperes, there were unmistakable evidences of tetany and a very distinct reduction in the calcium of the serum. This is another way of demonstrating the specificity of the cathodal hyperexcitability of Thiemich and Mann which, from clinical experience, has been considered satisfactory evidence of the presence of tetany.

The influence of calcium upon the symptoms of tetany has been studied in two ways. Bogen, Risel, Rosenstern, von Pirquet, Zybelle and others gave calcium in various forms and in various doses; but they gave usually only one dose and determined the effect of its administration upon the electrical reactions. From the single dose no effect or only a temporary effect, upon the clinical symptoms was observed. Others, notably Netter and Göppert, have consistently used calcium in the treatment of tetany and have reported striking results from its use, when repeated doses have been administered. Its usefulness has not been demonstrated except by the dissipation of clinical symptoms, *i. e.*, its effect upon the electrical reactions or upon the other signs has not been noted. With the proof that in active tetany the calcium in the serum is consistently low, it has been the logical thing to give calcium and to give calcium repeatedly, for if there is a constant calcium loss it is only by the continued administration of calcium that a sufficient quantity to prevent symptoms can be kept circulating in the blood. If the administration of calcium is interrupted it soon sinks again to its previous low level. We have, therefore, given calcium by mouth in doses of from 0.5

gm. to 1.0 gm. every 4 hours. We have also determined the effect of this administration of calcium upon the electrical reactions and upon the calcium content of the serum as well as upon the clinical symptoms. It may be stated without reservation that calcium has a very prompt effect in preventing all of the symptoms of active tetany. In the course of a few hours the symptoms diminish in intensity and almost always in 36 or 48 hours they have entirely disappeared. The electrical reactions also undergo an alteration so that C. C. T. or a C. O. C. with a current of less than 5 milliamperes is no longer obtained. The calcium content of the serum also rises. In some instances it has reached nearly normal in the course of a few days. In the majority of instances, however, it has not reached normal, but has remained between 7.5 and 9 mg. for a long time, despite the continued administration of calcium. The symptoms, however, have been held entirely in abeyance. We know of hardly another drug which acts in disease with the promptness and with the regularity that calcium does in tetany. The calcium administration must, however, be continued. The cessation of the drug for a few days, perhaps even hours, will allow the return of symptoms and it is altogether probable that in many instances it must be continued until in the ordinary course of events the tendency to tetany disappears. This is added evidence to us that the calcium deficiency in tetany is not a primary condition. It is brought about by some unknown factor which diminishes to a very marked degree the calcium content of the serum, which is operative chiefly during certain months of the year and which gradually loses its effect or disappears.

We employed calcium lactate at first. It did not appear to us that the effects were so prompt as those produced by calcium chloride. For this reason we have given calcium chloride in the great majority of instances. This has been administered in the food. We have continued the calcium in most instances for several weeks and have then gradually diminished the amount and frequency of administration until it was discontinued entirely.

It is undoubtedly true that in many instances phosphorus and codliver oil have a distinct effect in improving tetany. At times, however, their influence is slight. In any event it is slow and is often not sufficiently marked or sufficiently prompt to prevent the development of dangerous or perhaps fatal symptoms. Whilst, therefore, these substances are indicated they can by no means take the place of calcium. In the presence of severe or dangerous symptoms, chloral, morphine, and chloroform and magnesium sulphate hypodermatically must be used in sufficient amount and frequently enough repeated to hold the symptoms in check until calcium in full doses produces its sedative effect. This is usually within 36 or 48 hours. Thereafter only the calcium need be given. Further investigations will show whether the influence of phosphorus and codliver oil is similar to that of the calcium, and that when its administration is discontinued, the calcium in the serum again sinks to a low level, or whether it has a more fundamental effect than the calcium administration and over-

comes the factors that are responsible for the deficiency of circulating calcium.

Our conception of tetany is that some factor, at present unknown, causes a reduction of the calcium content of the blood. When this reaches an amount roughly between 6.0 and 7.0 mg. of calcium per 100 c. c. of serum, frank evidences of tetany arise. This amount, however, is not the same with all individuals. With some it may be as low as 5.5 or 6.0, with

others, as high as 7.5. These symptoms occur in outbursts so long as the calcium remains low. When the calcium rises the symptoms disappear. The height to which the calcium must rise in order that the symptoms must disappear is also somewhat variable. We believe that many of the symptoms are directly referable to the diminished calcium content of the blood and that they may be prevented or caused to disappear by repeated doses of calcium.

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# BULLETIN

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## THE DEVELOPMENT OF THE HUMAN VERUMONTANUM

By ERNEST M. WATSON, A. M., M. D., Buffalo, N. Y.

(From the James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore, Md.)

Our knowledge regarding the origin and more particularly the development and structural formation of the verumontanum is far from complete. In studying the literature one finds numerous references to the development of the Wolffian ducts and to the gross changes of the Müllerian ducts in their transformation to form the prostatic utricle or sinus pocularis. Beyond the mere recognition of Müller's tubercle or Müller's hillock on the dorsal surface of the urogenital sinus, however, there are practically no recorded observations on the growth and notably the developing glandular structure of the verumontanum. Accurate studies begin only with adult life.

The notation of the occurrence of a raised prominence on the floor of the posterior urethra in connection with the development of the Wolffian and Müllerian ducts was probably first made by Müller. Felix,<sup>1</sup> in his monograph on the Development of the Urinogenital Organs, in Keibel and Mall's System of Embryology, states: "The two excretory ducts remain close together and the region in which they open becomes raised up into a hillock and projects into the lumen of the urethra; this hillock we shall term Müller's hillock." This structure, in its later stages containing the sinus pocularis (fused Müllerian ducts of the female), the lower ends of the paired Wolffian ducts with their openings, together with various glandular tubules and inter-tubular stroma comes to form the verumontanum of later embryonic and of adult life.

Rudinger<sup>2</sup> and Henle<sup>3</sup> among the earlier writers described the gross picture of the veru quite at length. Concerning the prostatic utricle or sinus pocularis much has been written. Morgagni<sup>4</sup> first called attention to this structure contained within the veru and later Albinus,<sup>5</sup> Schlichting<sup>6</sup> and particularly Weber,<sup>7</sup> discussed in some detail its formation and especially the analogy between it and the uterus of the female.

Among the present-day writers the work of Rytina<sup>8</sup> on the histology and gross anatomy of the adult verumontanum is the most complete and comprehensive. Lowsley<sup>9</sup> in his studies on the development of the human prostate gland only briefly mentions the changing morphology of the verumontanum.

The material for this study was obtained in part from the Embryological Collection of the Carnegie Institute and in part from the Obstetrical Service and from the Pathological Department of The Johns Hopkins Hospital. In all eight human embryos were studied varying in age from the thirteenth week of fetal life until birth. The age of each was determined according to the table and classification of measurements in Keibel and Mall's<sup>10</sup> System of Embryology. The specimens were embedded in paraffine and serial sections were made through the genito-urinary tract of each specimen from the urachus to the anterior urethra. These were cut in varying thickness—6  $\mu$  and 15  $\mu$  in the younger and 40  $\mu$  in the older specimens. The sections were stained in hæmatoxylin

and eosin and every section was saved for study. The measurements of the various structures were made by means of a micrometer eye-piece for the lateral diameters and for the perpendicular height by counting the several sections, each of which was of a known thickness.

FETUS 80.3 MM. LONG (CR), 13 WEEKS OLD  
(No. 768c, Carnegie Collection)

Just below the internal vesical sphincter at a level where the proximal end of the prostatic utricle is first encountered the floor of the urethra is practically flat, while the lumen of the urethra as a whole is oval with the greatest diameter from left to right. The utricle is first found .7 mm. below the urethral floor as an elliptical cavity, viewed in cross-section, with its long diameter extending dorso-ventrally situated midway between the common ejaculatory ducts. These three structures, utricle and ejaculatory ducts, are surrounded by a mass of undifferentiated mesenchymatous cells which is somewhat poorly defined and blends without notable differentiation with the kindred cells going to form the intertubular prostatic tissue and the urethral walls themselves. The blood-vessels at this time occupy for the most part a position along the lateral margins of the cell mass and between it and the prostatic intertubular substance.

A few sections below this picture the mid-portion of the urethral floor shows a slight mid-line elevation with a consequent furrow at the base on either side. This furrow of elevation carries with it the mucous lining of the urethra composed of three layers of epithelial cells and below the undifferentiated mesenchymatous tissue going to form the urethral walls and the intertubular substance of the prostate. At this level there are no tubules of the middle lobe of the prostate demonstrable. As further sections are studied in order along the course of the posterior urethra an additional elevation is encountered on either side of the one noted above, lifting the urethral mucous membrane and underlying mesenchyme into two ridges resembling the one just described, although it is much smaller.

At the time of encountering these additional striæ of elevation there are several tubules of the middle lobe of the prostate noted situated midway between the first described elevation of the urethra and the ejaculatory ducts. During this progress through the sections the ejaculatory ducts have notably diminished in size and become practically round while the utricle has enlarged until now its diameter is twice that of the ejaculatory ducts and is pear-shaped or triangular in cross-section with its greatest width toward the dorsal surface of the prostate. The entire three structures in their course have come to occupy a position about the center of the prostatic tissue and have seemingly pushed the middle lobe tubules upward, well toward the urethral floor, where they are seen to open on either side of the middle elevation. At this point the middle and lateral elevations of the urethral floor merge into one rounded or half-moon-shaped structure composed of undifferentiated mesenchymatous tissue covered with the mucous lining of the urethra (which consists of several layers) and enclosing at its rather broad base the prostatic utricle and ejaculatory ducts. These in their upward slanting course have now reached the urethral level or base of the verumontanum. From here the structures take an upward slanting direction and the ejaculatory ducts finally open simultaneously on the sides of the verumontanum about its middle portion well up towards its summit. The utricle continues as a closed canal for only a few sections beyond the openings of the ejaculatory ducts where it ends as a blind pouch .1 mm. below the mucous surface of the verumontanum. The veru continues for about .3 mm. beyond the last vestige of the utricle and finally fades away in three slim elevated ridges or striæ as in its origin from the floor of the urethra above.

The veru measures about .7 mm. in length in this specimen from its origin in the striæ just outside the internal sphincter to its end in the small similar folds extending down toward the membranous urethra. Its height is .4 mm. at the most prominent portion which is above and anterior to the openings of the ejaculatory ducts and where the ducts and utricle first reach the base of the veru on their upward slanting course through this organ. The width of the veru at its widest point, which is also at the site of greatest height, is .7 mm., making it of equal length and breadth at this stage. The prostatic utricle extends as a hollow tube lined with mucous cells one or two layers deep for a little over .4 mm. coursing through the prostate gland in an upward slanting direction.

The cavity of the utricle is somewhat cigar-shaped and on cross-section tends to be oval, measuring about  $\frac{1}{4}$  by  $\frac{1}{10}$  mm. in diameter. At this stage the veru is made up of a mass of undifferentiated mesenchymatous cells budding forth from the mid-ventral portion of the urethral floor and pushing the urethral mucous membrane before it. Its cells cannot be differentiated from those forming the intertubular substance of the prostate itself. There is no evidence of any tubular elements in the verumontanum as yet, but above are a few tubules of the middle lobe of the prostate which may be seen entering the urethra along the prostatic furrows sometime before the openings of the ejaculatory ducts are encountered.

The walls of the ejaculatory ducts are composed of undifferentiated mesenchymatous cells, which are as yet not unlike those going to form the substance of the veru itself. At the openings of the ejaculatory ducts into the urethra there is no suggestion of any change in the arrangement of the cells, but here the mucous lining of each duct is approximated so that the lumina of the ducts are filled in. The cells going to form the veru even at this state are more closely packed and take the stain more deeply than those of the intertubular substance of any of the prostatic lobes, a fact indicating embryologically that they are perhaps a little older or were laid down a little earlier than the prostatic stroma.

FETUS 105 MM. LONG (CR), 14 WEEKS OLD  
(No. 1358c, Carnegie Collection)

The three striæ arising from the urethral floor entering into the formation of the verumontanum above are less marked in this specimen. In fact, the middle elevation is the only one that can be readily recognized. At the first level of its identification, however, the tubules of the middle and two lateral lobes of the prostate and also of the anterior lobe are well formed. The urethra in this specimen is cone-shaped with its base corresponding to the floor of the urethra. The veru at this time is well formed and at its upper portion near the internal sphincter is an almost pedunculated organ in cross-section. Its upper surface is covered with a mucous membrane having several layers and continuous with that lining the urethra. Over the veru, however, this mucous covering is quite irregular in outline, dipping down in places to form notable pits and in some places forming a series of pockets which become shut off from the lumen of the urethra and appear as definite tubules of the outer portion of the verumontanum.

This irregularity is first noted at the tip of the veru, but in the succeeding sections it is seen to extend well down on either side to the prostatic furrows. The prostatic utricle is first observed at the base or urethral level of the veru as a slit-like aperture with its long diameter extending dorso-ventrally, while on either side are situated the common ejaculatory ducts. The utricle is lined with a several-celled layer of mucous cells in all respects similar to those lining the ejaculatory ducts.

About the utricle and ducts the mesenchymatous cells are a little more closely packed and somewhat more deeply staining than in other portions of the veru. The utricle and ducts continue an upward slanting course through the substance of the



veru and the ducts finally open into the urethra on either lateral aspect of the veru very near its summit. The utricle continues for a few sections beyond these openings and then ends as a blind pocket nearly .5 mm. below the mucous membrane of the veru. The utricle is about .6 mm. long in this specimen and .3 mm. in its greatest diameter, which is dorso-ventrally, while its walls are approximated throughout its entire course. From all points the utricle is essentially only a verual organ in this specimen at this stage. The verumontanum measures approximately .7 mm. long and .7 mm. in diameter in its widest portion, while its highest point is 1.3 mm. from the urethral floor.

The composition of the veru is still for the most part undifferentiated mesenchyme, while the walls of the ducts and utricle show simply a more close approximation of cells and as yet no definite musculature. The peripheral tubules are present, seven on the left side and four on the right, formed from infoldings of the mucous covering.

An interesting finding in this specimen shows the tip of the veru in its lower third securely attached to the roof or dorsal aspect of the urethra. This condition is apparently rare if not constituting a real anomaly, as it has not been observed in any of the other specimens studied.

FETUS 130 MM. LONG (CR), 16 WEEKS OLD  
(No. 1018, Carnegie Collection)

As soon as the internal sphincter is passed the longitudinal striæ which merge to form the upper surface of the veru are encountered. The middle fold is first noted, being somewhat longer than the other two situated one on either side of it. At the level where the striæ are first observed there are present the tubules of the middle and two lateral lobes of the prostate, but none of the anterior are seen. The middle fold increases in size in its course down the urethra and finally the lateral folds become a part of it. At the level where the veru may be said to begin the ejaculatory ducts are .5 mm. below the urethral floor with a few middle-lobe tubules between these two points. The urethra is somewhat star-shaped with the veru projecting well into its lumen. The irregularity of the mucosa covering the veru is noted again in this specimen forming well-defined pits, though this is not so marked as in the previous specimen.

The utricle is first encountered just below the urethral level and at the base of the veru as a somewhat irregular opening, but in general circular in outline measuring about .1 mm. in diameter situated .25 mm. below the surface of the veru. It is lined with mucous cells one or two layers deep. Immediately beneath the mucosa covering the veru the previously undifferentiated cells have now become more specialized and here form a well-defined covering over this organ of an early stroma-like sheath. Within this sheath are included the utricle and the two ejaculatory ducts which are still surrounded by a mass of clearly undifferentiated mesenchymatous cells. This stroma-like sheath can easily be traced down to the somewhat similar intertubular structure of the prostate gland with which its fibers are closely intermingled. Within this stroma are here encountered for the first time several tubules or gland acini which come to lie along the sides of the now well-formed verumontanum. In tracing these structures through the veru it is seen that they first occupied a position as a part of the sub-urethral portion of the prostate middle lobe and have seemingly been pushed upward to occupy their new position by the upward growth of the verumontanum. At this time also is noted the definite fibrous elements in and about the walls of the utricle and ejaculatory ducts. All tubules observed open into the urethra along the sides of the veru and in no instance have any tubules of prostatic origin been observed opening into either the utricle or ejaculatory ducts.

Through the veru the ducts and utricle pursue an upward slanting course and all assume an elliptical outline in cross-section.

This is brought about to a considerable extent by the pressure from either side by the formation of the stroma-like sheath and the growth of several tubules within this enclosure. The ejaculatory ducts first occupy a position below the utricle at the upper level of the veru just beneath the termination of the superior striæ. In their course downward, however, they become separated and, before the mid-verual portion is reached, come to occupy a position on either side of the utricle. At this time the utricle appears as a longitudinal slit lined with mucous membrane and its walls approximated. It measures at this time .4 mm. in its dorso-ventral diameter.

Continuing their course upward the ducts decrease in size and finally, about the mid-portion of the veru, open through the sides of this organ very near its tip into the urethra. The utricle continues for a few sections beyond the openings of the ejaculatory ducts where it ends as a blind pouch .05 mm. beneath the mucous membrane of the veru. The utricle measures a little over .6 mm. in length in this specimen and is sword-shaped with its walls approximated and the greatest diameter extending dorso-ventrally. After the openings of the ejaculatory ducts are passed and beyond the utricle the verumontanum becomes a highly tubular organ. This is caused by the tubules of the middle lobe (prostate) seemingly pressing upward, so that some five or six of them have come to occupy a position in the veru giving it a decided honeycombed appearance in cross-section. After this has continued for some distance, these tubules of prostatic origin disappear and over the lower or inferior third of the organ only the infoldings arising from invaginations of the mucous covering are seen, while the extreme inferior portion of the veru has no tubular elements. As in the earlier specimen the veru gradually fades away into three or possibly four small but definite striæ of elevation, which are observed decreasing in prominence as they are traced down the prostatic urethra toward the external sphincter. The veru measures 1.25 mm. long and .6 mm. wide in its greatest diameter, while its greatest height is .4 mm. at the level of the openings of the ejaculatory ducts.

FETUS 171.4 MM. LONG (CR), 19 WEEKS OLD  
(No. 1049, Carnegie Collection)

The utricle is first encountered in this specimen fairly high up, before there is any indication of the formation of the veru or before even the superior striæ are noticed. It is observed as an irregular star-like cavity lined with a mucous membrane of several layers and with its walls approximated. It measures .4 mm. by .1 mm. in diameter in cross-section, the greatest width extending dorso-ventrally, and lies .5 mm. below the urethral floor. Just dorsal and on either side of it are situated the ejaculatory ducts which are about the same size as the utricle, but with their walls well dilated. Between the utricle and urethral mucosa are observed several tubules (six or seven of the middle prostatic lobe, the sub-urethral portion). Also in their respective areas about the urethra are noted the tubules of the anterior, and the two lateral lobes, and also those of the posterior lobe.

The intertubular substance of the prostate is here well defined as an unmistakable stroma. A few undifferentiated mesenchymatous cells still remain grouped about the utricle, but about the ejaculatory ducts the differentiation into a muscular coat is observed. On either side of the mid-line the urethral floor with its mucosa is slightly elevated for a short distance appearing as two striæ. The middle fold described in the three previous specimens is here lacking. These two striæ are soon lost in the general elevation of the mid-urethral floor by the pushing up of the veru. The stroma-like sheath marking the boundaries of the veru, mentioned in the previous specimen, is here still more strikingly shown, and within this the undifferentiated mesenchyme still persists, yet in the region about the utricle it has begun to take on a somewhat stroma-like aspect.

In following the ejaculatory ducts through the prostate they decrease in size as in the previous specimen and become elliptical in outline, their long diameter extending dorso-ventrally. The mucosa over the superior third of the veru is still somewhat irregular with moderate invaginations and pit formation. This irregularity is not so marked as in the specimens at 14 and 16 weeks, but is still quite evident. In their course through the veru the ejaculatory ducts and utericle pursue an upward, slanting path and the ducts finally open simultaneously in the mid-portion of the veru well up toward its tip. Even at this time there is scarcely to be noted a definite musculature to their walls, but merely a more deeply staining layer of cells which somewhat resemble stroma cells. The utericle extends only a few sections beyond the openings of the ejaculatory ducts where it ends as a blind pocket .05 mm. below the mucous membrane covering the veru. The utericle measures 1.2 mm. long in this specimen and runs as a sword-like canal with its walls for the most part approximated.

Beyond the openings of the ejaculatory ducts and the distal portion of the utericle the veru is made up very largely of tubular elements having their origin from the sub-urethral portion of the middle lobe. These with a relatively small amount of stroma and only a slightly irregular mucous membrane go to make up the organ. All tubules open on either side of the veru along its inferior third directly into the urethra. Beyond the openings of the ejaculatory ducts the tubules are more numerous, but in the superior or upper portion those of prostatic origin can be definitely made out. After the region of the tubules is passed the inter-tubular stroma of the veru continues for a short distance down the urethra as a central ridge and is finally lost in the floor of the urethra. The lateral inferior striæ were not found in this specimen. The veru at this time measures 2.5 mm. in length, .5 mm. in height and .9 mm. in width along its greatest diameter.

FETUS 178 MM. LONG (CR), 21 WEEKS OLD

(No. 1171, Carnegie Collection)

In this specimen the superior striæ are present and well developed. The middle elevation is most prominent and on either side are two definite folds resembling to a considerable degree the picture seen in the previous specimen. The folds are covered with mucous membrane three- or four-cell layers deep, while the underlying stroma is seen extending well into each elevation. The utericle is first encountered .5 mm. beneath the superior striæ before the real urethral elevation of the veru is observed. It exists as a circular cavity, .4 mm. in diameter, situated just above the common ejaculatory ducts, which are here circular cavities .3 mm. in diameter. Both between the ejaculatory ducts and utericle on the one side and between the utericle and urethra on the other are observed several tubules of the prostatic middle lobe.

The superior striæ continue over the upper third of the veru in this specimen and are finally lost in the irregularities of the mucous membrane. This irregularity, as in the earlier specimens, has now become quite characteristic of the upper third of the veru. It is traced into pits and in the deeper portion to definite tubule formation. These tubules arising from the urethral mucosa occupy a position about the extreme periphery of the organ. The glands from the prostate (middle lobe), previously mentioned as lying above the utericle, are in the progress of the upward slanting course of the utericle and ejaculatory ducts gradually pushed upward until they become gland tubules of the veru itself. Here they occupy a position along the lateral walls of the organ beneath those tubules derived from the infolding urethral mucous membrane. These deeper tubules derived from the prostatic middle lobe finally open into the urethra along the lateral walls of the veru itself.

In the course through the veru, after the superior third of the organ is traversed, the utericle becomes much smaller and its

lateral walls become approximated with the ejaculatory ducts situated on either side of it. All three structures are at this level elliptical in outline with the greatest diameter extending dorso-ventrally. Without further notable change the ejaculatory ducts continue their upward slanting path and finally open up on either side of the veru well up toward its tip. The walls of the ejaculatory ducts are in this specimen well defined throughout and the changing mesenchymatous cells which make up their walls are well observed by their elliptical shape and their more densely staining properties. The utericle continues as a closed canal a few sections beyond the openings of the ejaculatory ducts and there ends as a blind pocket .1 mm. below the mucous membrane covering the veru.

The utericle is cigar-shaped in this specimen and measures about 1.4 mm. in length. Below or inferior to the openings of the ejaculatory ducts the veru is made up of a few tubules having their origin from the prostatic middle lobe. These are here few in number (about five or six) and soon end by opening into the urethra along the sloping sides of the veru. The remainder of the veru is made up entirely of stroma having a mucous covering similar to the urethra itself. In tracing the veru down toward the membranous urethra it is seen to fade away in three striæ or folds which soon decrease to the level of the urethra. The veru measures 1.4 mm. long, .7 mm. high and 1 mm. in width at its widest point.

FETUS 221 MM. LONG (CR), 25 WEEKS OLD

(No. 1172, Carnegie Collection)

Along the superior or upper portion of the urethra the striæ which merge to form the veru are clearly delineated as three well-marked folds. The middle elevation is the most prominent, but in all three the basal stroma extends well into the substance of the folds as a series of conical peaks. The mucous covering is here, as in the previous specimens, several layers thick and along the sides of the veru the indentations and pit-formation are well defined. In certain areas tubule formation from the invaginating mucous membrane covering is readily recognized. These tubules occupy the periphery of the organ. Beneath these structures are scattered the tubules of the sub-urethral portion of the middle lobe of the prostate which have been pushed upward to occupy a position in the substance of the veru itself.

The utericle when first encountered occupies a position entirely within the veru as an elliptical cavity .6 mm. below the surface of the urethra and measures .5 mm. by .3 mm. in diameter. The ejaculatory ducts at this level occupy a position dorsal and to either side of the utericle as irregular, somewhat star-shaped cavities lined with mucous membrane. The stroma at this stage is very prominent in the structure of the veru, surrounding all tubules and forming a well-defined capsule about the utericle and ejaculatory ducts. Within this capsule there still remains a small amount of poorly differentiated mesenchyme, but that entering into the formation of the walls of the ducts and utericle has very nearly the appearance observed at birth.

In this course through the veru the utericle and ejaculatory ducts become considerably elongated or elliptical in cross-section and all three structures finally come to lie parallel with their long axes extending dorso-ventrally. At this time is noted for the first time an evagination and pit-formation from the walls of the utericle and to a very slight extent from those of the ejaculatory ducts also. This irregularity of their mucous lining gives these structures a definitely pocketed appearance in cross-section. A little beyond the level of this irregularity of their lining the ejaculatory ducts are seen to open on the sides of the urethra well up toward its tip. Their mouths are wide open with no suggestion of any sphincteric fibers at their orifices. The utericle extends a few sections beyond the openings of the ejaculatory ducts, but



there ends as a blind pouch .05 mm. beneath the mucous covering of the veru.

In this specimen is observed the pointed evagination of the ventral surface of the utricle toward the urethral lumen, directing its subsequent path of opening into the urethra. The utricle measures .5 mm. in length by .1 mm. in diameter at its greatest width and is confined entirely as a closed cavity within the veru. Beyond the openings of the ejaculatory ducts the veru is made up of several tubules of prostatic origin, which open along the sides of the urethra. These are surrounded by an abundance of intertubular stroma which is supplied with numerous blood-vessels. After the tubules are passed, the stroma with its rich blood supply makes up the entire verual elevation. The veru finally diminishes into three slight but definite folds, the inferior striae, which gradually reach the urethral level toward the membranous urethra. The veru measures at this time 2 mm. long, 1 mm. high and 1.7 mm. wide.

#### FETUS 276 MM. LONG (CR), 31 WEEKS OLD

(No. 7, Obstetrical Service of The Johns Hopkins Hospital)

The three superior longitudinal striae are encountered at their beginning just below the internal sphincter in this specimen. They are covered with several layers of mucous membrane and, as in the previous specimen, the stroma extends well up into each elevation. Close beneath the striae are several tubules of the middle prostatic lobe which later appear in the veru itself, well separated from the other middle lobe tubules. In following the sections down through the prostatic urethra the superior striae are soon lost in the general elevation of the veru, which here is composed of numerous tubular nests closely bound around with stroma. All of the above-mentioned tubules open along the sides and a few at the summit of the veru.

The utricle first appears as a circular cavity 2.5 mm. below the surface of the veru and is .3 mm. in diameter. It is situated between the ejaculatory ducts which are quite irregular in outline and are approximately half the size of the utricle itself. The superior or upper third of the veru is composed very largely of the tubular elements derived from the infolding mucous membrane covering the veru, and its ventral surface is above extremely irregular owing to this infolding and pit-formation of the invaginating mucosa. In its course through the prostate the utricle increases in size and becomes irregular while the ejaculatory ducts on either side rapidly diminish in diameter and tend to become circular in outline.

When first observed the utricle and ejaculatory ducts are clearly walled off within a very definite stroma capsule and this persists about these structures during their course through the prostate gland. The sub-verual structures become thinned out in this specimen and the veru and utricle seem to approach each other by a thinning out of the intermediate tissue more than by a course through the prostate. At this level the few middle-lobe tubules, which eventually become a part of the verual gland tissue, are easily recognized and appear just above the utricle and are literally pushed up by it to their new position in the veru. The peripheral verual tubes from their origin from the infolding of the urethral mucosa are here well separated from the tubules of prostatic origin by a well-defined area of stromal tissue.

In tracing the varied structures through the veru the utricle is seen to become quite irregular in outline and in places almost star-shaped in cross-section. The evaginations from its main walls to form tubules are few, less numerous than in the preceding specimen, and are located for the most part between the utricle and ejaculatory ducts. All the structures finally open spontaneously into the posterior urethra, the utricle at the summit of the veru in the mid-line and the ejaculatory ducts on either side of the opening of the utricle. The utricle gives an

almost double-duct appearance at this level by its great irregularity, possibly of significance from its origin from the paired Müllerian ducts of the female. About the openings of the ejaculatory ducts there is no evidence of any isolated fibers that might have a sphincteric action. Both orifices are free and gaping.

The opening of the utricle extends several sections further than the openings of the ejaculatory ducts. The utricle in this specimen is 3.5 mm. long. Beyond the duct openings and utricle the veru is composed of several lateral tubules of prostatic origin which soon open into the urethra through the mucous membrane of the veru. The remainder of the veru is made up of a dense stroma which is well supplied with blood-vessels. The inferior fourth of the veru is practically free from tubules of any type. The veru finally ends by decreasing into four ridges of elevation, the inferior striae, which are lost in the floor of the urethra. The veru is 4.25 mm. long, .3 mm. high and 1.4 mm. wide at its greatest diameter.

#### FETUS 338 MM. LONG (CR), AT BIRTH

(No. 8, Pathological Department of The Johns Hopkins Hospital)

As in the preceding specimens, the floor of the prostatic urethra in its upper portion presents essentially the same three elevations previously termed the superior striae. The middle elevation is here the largest and all three have their origin soon after the last of the sphincteric fibers are passed. Each is covered with mucous membrane several cell layers deep, below which is the stroma extending well up into each elevation. Even at the level of the superior striae the irregularity of the mucous covering is present and beneath the surface the definite tubules of the veru arising from this infolding or pit-formation is well demonstrated. The tubules of the middle prostatic lobe at this time are situated somewhat deeply beneath the urethral floor just above the irregular ejaculatory ducts and well separated from the first-mentioned tubules by a rather thick layer of stroma tissue.

In their course down the urethra the superior striae soon lose their identity and become fused with the middle elevation, which then becomes the upper portion of the verumontanum. At this level the prostatic utricle is first encountered as a somewhat irregular circular aperture .2 mm. in diameter, lined with mucous membrane several cell layers deep, surrounded by numerous strands of loosely packed stroma. Beyond this is the more definite stroma capsule which contains the tubules of mucous membrane origin, some three or four on each side situated along the lateral margins of the veru. In its path through the veru the utricle becomes quite irregular, its mucous lining evaginating well into the adjacent stroma to form well-defined tubules, all of which empty into the utricle itself. The outer series of verual tubules of mucous membrane origin all empty into the prostatic urethra along the sides of the veru. At this level, the superior or upper third of the organ, the tubules of true prostatic origin (middle lobe) have not taken a place in the substance of the veru itself.

In the following sections the ejaculatory ducts are traced upward through the substance of the prostate, gradually becoming smaller, although still maintaining their rather marked irregularity of outline. In their upward course they are observed literally pushing up into the substance of the veru several tubules of prostatic origin. These later become pushed to either side of the veru and finally open up into the prostatic urethra on either side of the veru. At this level the tubules of mucous membrane origin have practically all disappeared, for they occupy for the most part only the superior third of the veru. Traversing the substance of the veru the outline of the utricle becomes more and more convoluted and its ensuing tubule formation becomes more marked so that at the level of its opening into the posterior urethra there is a veritable nest of tubules emptying into its lumen for the most part along the mid-line but to some extent also along its lateral



walls. The utricle opens into the urethra before the ejaculatory ducts and while the latter structures are still elliptical lumina on either side of the utricle lying a little less than .3 mm. below the urethral floor. From this picture the ejaculatory ducts pursue a rapid course upward toward the tip of the veru and finally open on the upper lateral walls of the organ on either side of the opening of the utricle. The utricle measures .3 mm. long and, although very irregular, tends to be sword-shaped and measures 1 mm. by .2 mm. in diameter.

At this level and in the succeeding slides the tubules of prostatic origin become more numerous and practically comprise the entire veru except for the few supporting strands of intertubular stroma. This picture continues for only about the third quarter length of the veru, after which a mass of stroma tissue comprises the remaining or last quarter length of the organ with only a rare tubule opening along its lateral margin. Finally, the veru fades away into three rather ill-defined elevations or striæ, which eventually become lost as they approach the level of the urethral floor in the direction of the external sphincter. The veru in this specimen is nearly 4 mm. long, 1 mm. high and 1.5 mm. wide in its greatest width.

#### SUMMARY

(1) At the thirteenth week of foetal life the verumontanum is merely a rounded elevation arising from the posterior urethral floor. It is composed of undifferentiated mesenchymatous cells and covered with mucous membrane. Three striæ merge above to form its elevation and the same number are encountered below at its termination. It has no tubular elements and measures .7 mm. in height and the same in breadth at its widest portion. It contains the prostatic utricle and the terminal portions of the ejaculatory ducts.

(2) By the fourteenth week definite glandular tubules of the veru have appeared, arising from invaginations of its mucous covering and occupying a definite position about the periphery of the organ. These tubules open into the posterior urethra. The prostatic utricle is contained entirely within the veru in this specimen.

(3) A second group of tubules of the veru appear by the sixteenth week. These are prostatic in origin, arising from the suburethral portion of the middle lobe. They occupy a position just below the outer strata of peripheral tubules and all open into the urethra along the middle third of the veru.

(4) The nineteenth week of foetal life brings no material change in the character of the elements entering into the formation of the veru other than observed in the preceding specimens. The tubules of prostatic origin are, however, more numerous.

(5) At the twenty-fifth week the peripheral tubules arising from the invaginating mucous membrane and also the middle strata tubules of prostatic origin are readily identified. In addition irregularities of the walls of the prostatic utricle and to some extent of the ejaculatory ducts are observed, with tubule-formation from the evaginating lining of the utricle.

(6) The utricle opens into the posterior urethra at the summit of the veru between the twenty-fifth and thirty-first week. At the later date the three groups of tubules entering into the formation of the veru are clearly identified.

(7) At birth the veru measures 4 mm. long, 1 mm. high and 1.5 mm. in width. It is a highly glandular organ and the

three sets of tubules, (a) those about the upper portion and periphery arising from the invaginating urethral mucosa, (b) those situated in the middle and lower portion arising from the prostatic middle lobe, and (c) those about the utricle arising from the evaginating mucous lining of the utricle are easily recognized. It contains also the terminal portions of the ejaculatory ducts and the prostatic utricle.

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#### DESCRIPTION OF PLATES

FIG. 1.—Spec. No. 768c, Carnegie Collection. Fœtus 80.3 mm. long, 13 weeks old. Transverse section through the upper limit of the verumontanum. A. Central superior stria. B. Tubules of the prostate gland (middle lobe).

FIG. 2.—Spec. No. 768c, Carnegie Collection. Fœtus 80.3 mm. long, 13 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts opening into the prostatic urethra. No inherent glandular tubules are noted at this stage.

FIG. 3.—Spec. No. 1358e, Carnegie Collection. Fœtus 105 mm. long, 14 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Early invagination of the mucous covering to form the peripheral tubules.

FIG. 4.—Spec. No. 1358e, Carnegie Collection. Fœtus 105 mm. long, 14 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Fibrous strands firmly attaching the tip of the veru to the roof of the urethra (an anomaly). D. Peripheral gland tubules of mucous membrane origin.

FIG. 5.—Spec. No. 1018, Carnegie Collection. Fœtus 130 mm. long, 16 weeks old. Transverse section through the upper portion

of the verumontanum. A. Undifferentiated mesenchyme of the veru. B. Peripheral tubules of mucous membrane origin. C. Pitting of the mucous covering to form tubules.

FIG. 6.—Spec. No. 1018, Carnegie Collection. Fœtus 130 mm. long, 16 weeks old. Transverse section through the lower third of the verumontanum. A. Prostatic utricle. B. Opening of the common ejaculatory ducts into the urethra. C. Gland tubules of prostatic origin (middle lobe) entering into the base and sub-peripheral portion of the veru.

FIG. 7.—Spec. No. 1049, Carnegie Collection. Fœtus 171.4 mm. long, 19 weeks old. Transverse section through the upper portion of the verumontanum. A. Prostatic utricle surrounded by a beginning stroma-like sheath. B. Common ejaculatory ducts. C. Gland tubules of mucous membrane origin.

FIG. 8.—Spec. No. 1049, Carnegie Collection. Fœtus 171.4 mm. long, 19 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Gland tubules of prostatic origin (middle lobe).

FIG. 9.—Spec. No. 1171, Carnegie Collection. Fœtus 178 mm. long, 21 weeks old. Transverse section through the upper portion of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Gland tubules of mucous membrane origin.

FIG. 10.—Spec. No. 1171, Carnegie Collection. Fœtus 178 mm. long, 21 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Gland tubules of mucous membrane origin. D. Gland tubules of prostatic origin (middle lobe).

FIG. 11.—Spec. No. 1172, Carnegie Collection. Fœtus 221 mm. long, 25 weeks old. Transverse section through the tip of the verumontanum. A. Prostatic utricle showing the irregularity of its lining membrane. B. Common ejaculatory ducts showing the

irregularity of their walls. C. Gland tubules of mucous membrane origin.

FIG. 12.—Spec. No. 1172, Carnegie Collection. Fœtus 221 mm. long, 25 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle pointing its subsequent path of opening into the urethra. B. Common ejaculatory ducts. C. Gland tubules of utricular origin, formed from the evagination of the walls of the utricle. D. Gland tubules of prostatic origin.

FIG. 13.—Spec. No. 7, J. H. Hosp. Obstet. Service. Fœtus 276 mm. long, 31 weeks old. Transverse section through the upper portion of the verumontanum. A. Prostatic utricle. B. Common ejaculatory ducts. C. Gland tubules of mucous membrane origin. D. Gland tubules of utricular origin.

FIG. 14.—Spec. No. 7, J. H. Hosp. Obstet. Service. Fœtus 276 mm. long, 31 weeks old. Transverse section through the middle of the verumontanum. A. Prostatic utricle opening into the urethra. B. Openings of the common ejaculatory ducts. C. Opening of a gland tubule of prostatic origin. D. Gland tubule of utricular origin, later opening into the prostatic utricle.

FIG. 15.—Spec. No. 8, J. H. Hosp. Path. Service. Fœtus 338 mm. long, at birth. Transverse section through the tip of the verumontanum. A. Opening of the prostatic utricle into the urethra with tubules entering it in the mid-line. B. Common ejaculatory ducts. C. Gland tubules of utricular origin. D. Gland tubules of prostatic origin (middle lobe). E. Tubule of mucous membrane origin.

FIG. 16.—Spec. No. 8, J. H. Hosp. Path. Service. Fœtus 338 mm. long, at birth. Transverse section through the lower portion of the verumontanum beyond the openings of the utricle and ejaculatory ducts. A. Openings of peripheral gland tubules of mucous membrane origin. B. Gland tubules of prostatic origin (middle lobe).

## ELECTROMYOGRAPHIC STUDIES OF CLONUS

By STANLEY COBB

(From the Neurological Laboratory of the Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital)

Clonus has been studied graphically by many investigators, but their results have not been uniform because mechanical methods were relied on until the introduction of electromyography. In the present work a few cases were studied intensively by means of the string galvanometer and the results seem to show that clonus gives a typical electromyogram, the details of which perhaps throw light on the nature of clonus. Beginning slowly, the periods between contractions soon shorten to a constant length, and this periodicity then varies not at all with fatigue, and only slightly with change of muscular tension. Clonus was kept up for half an hour in one case. In different individuals the average length of these periods varies only by a few hundredths of a second, the shortest being .12 second and the longest .17 second. From the theoretical standpoint the coincidence of this rate of clonus with the rate of other organic tremors brings to mind interesting speculations in regard to the nature of intrinsic neuro-muscular rhythms.

### LITERATURE

The study of clonus by graphic methods dates as far back as 1850, when Alexander James<sup>10</sup> recorded the contractions mechanically. In the next few years Horsley,<sup>8</sup> Gowers,<sup>9</sup> and MacWilliam<sup>11</sup> did similar work, using either levers or tambours

connected with the moving foot. All of them report the rate of clonus to be between seven and ten per second, except MacWilliam, who records one case with a rate of 14. Examination of his records, however, shows that the waves are in pairs, and he himself states that this fast rate was recorded with the tambour attached directly to the contracting muscle, whereas the foot was vibrating simultaneously at a rate of seven. This 14 rate, therefore, is evidently an artefact due to the mechanical arrangement of the tambour.

In the years 1904-1907, four other investigators repeated and enlarged upon this earlier work. Their interest hinged largely on the making of a differential diagnosis between "hysterical" and "true" clonus. In their cases of true clonus the rate averaged between five and seven per second. Claude and Rose<sup>2</sup> found that six per second was the usual rate. Axenfeld<sup>1</sup> called it six or seven and found that Jendrassik reinforcement increased the rate. Levi<sup>3</sup> worked on 15 different individuals and found the usual rate to be six or seven, with one case as low as five per second. He states that fatigue increased the rate. His studies on clonus in normal and in hysterical individuals showed that they gave a much more irregular curve than that registered by the organic cases. Eshner<sup>4</sup> also found the rate in organic cases to vary between

5.8 and 8.0 per second, and showed that reinforcement increased the rate.

In the last few years three workers have applied the string galvanometer to this study. Wertheim Salomonson<sup>22</sup> examined several cases of organic disease and made simultaneous electromyographic and mechanical records, which show that the electrical discharge comes at the beginning of the muscular contraction. He found the rate of ankle clonus to be about eight per second, and shows a most interesting record of an hysterical clonus in which there is a continuous tetanus-like series of small waves underlying the larger waves that appear with the clonic muscular contraction.

Gregor and Schilder<sup>8</sup> made electromyograms of the muscular contractions in many forms of nervous disease; among others they show records of patellar and ankle clonus. These are at the rate of 7 to 9.5 and some of the individual contractions give several small action-currents. They mention this point as characteristic, thereby differing from Salomonson<sup>22</sup> who says that there is but one action-current for each clonic contraction. In an earlier paper<sup>7</sup> they had stated that there was but one "impulse" for each clonic contraction. All three of these authors speak of the action-currents as synonymous with the "Innervationsimpulse," an interpretation taken from Piper<sup>24</sup> who did the pioneer work in electromyography.

#### METHOD

The apparatus used for recording the action-currents of the muscles studied was the string galvanometer designed by Dr. H. B. Williams and manufactured by C. F. Hindle & Co. This is a standard machine such as is used in "heart stations" for electrocardiographic work. The optical system and recording camera were also the stock type made by this company, except that a special gear was introduced to give greater speed to the film; with this addition a speed of from 20 to 27 cm. per second was obtainable. For electromyographic work of this kind any string galvanometer might be used with slight adaptation; descriptions of such modifications are given by Williams,<sup>10</sup> Snyder<sup>17</sup> and Forbes.<sup>4</sup> The string used was the one supplied with the apparatus and consisted of a gilded quartz fiber 3 micra in diameter with a resistance of 5000 ohms.

Electromyography, or the study of the action-currents of the skeletal muscles, has been described from the physiological standpoint by Piper,<sup>24</sup> but a short description of the method as applied to the study of clonus may be inserted here:

In order to record the electrical changes in a contracting muscle a continuous circuit must be established through that muscle and the string of the galvanometer; thus there must be two electrodes on the body surface, one connected with each end of the string. One of these is applied to the skin just over the belly of the muscle to be studied, and the other is placed over some nearby skin area beneath which there is no muscular contraction. For example, in studying ankle clonus, one electrode is placed over the belly of the gastrocnemius and the other in the popliteal space. In patellar clonus one is over the rectus femoris about 20 cm. above the patella in the mid-line, while the other is fastened to the inner side of the leg about

6 cm. away, over a spot where no muscular contraction takes place during patellar clonus. In this way action-currents of the clonus are alone recorded.

In studying ankle clonus the subject lay prone with the knee-joint fully extended. The skin was washed with soap and water, dried with ether, and the electrodes were then applied to the points designated above. These electrodes were of the non-polarizable type described by Piper<sup>24</sup> and by Forbes.<sup>4</sup> They consist, briefly, of funnels filed off at the small end so as to admit a rubber stopper; a piece of cat's bladder is stretched over the larger end, and a zinc rod is thrust through the rubber stopper into the cell which is filled with a saturated solution of zinc sulphate. The leads from the galvanometer string are attached to these zinc rods and the solution, permeating the animal membrane, makes the necessary electrical connection with the body of the patient.\*

With the patient in position and the skin prepared, the electrodes are firmly fastened to the appropriate spots with narrow roller bandages. The galvanometer is then set with the string at such a tension that 1 millivolt causes a deflection of 1 cm. on the record. The connections are made with the patient; the resistance of the patient is measured and compensated, and the camera and lights are arranged for the making of the record. Then an assistant sets up ankle clonus by pressing sharply on the ball of the foot. In the case of patellar clonus the procedure is the same except that the patient lies supine and pressure is exerted on the patella to set up contractions in the rectus femoris.

When stimulation was kept up over a long period of time, as in the fatigue studies, it was found that the assistant became tired before the clonus, so it was necessary for the galvanometer operator to change places with him every five or ten minutes. This gave a short hiatus in the continuity of the clonus, but not of long enough duration to admit of much recovery from fatigue.

In some experiments the effect of a light pressure on the ball of the foot was compared with that of strong pressure. No accurate quantitative measurement of these variations in stimulation was attempted because only the grosser variations seemed to cause any corresponding changes in the periodicity, rate, and size of the action-current.

In relation to the leaking out of the zinc sulphate solution from the electrodes an interesting artefact was noticed which has been considered as possibly a physiological manifestation by Wertheim Salomonson.<sup>22</sup> In his records of clonus, he noticed that sometimes there was a slow wave following the quick action-currents. In the present experiments it was found that such slow curves always appeared when the solution leaked out of the electrode, allowing the membrane to

\* The leaking out of the zinc sulphate solution was often troublesome. An easy way to overcome this was devised by placing a funnel of slightly larger size tightly over the completed electrode and filling in the space between the two funnels with celloidin, thus effectively sealing up the loose connection between the cat's bladder and the inner funnel.



retract slightly from the skin and thus to cause a change of contact with each movement of the underlying muscle. Accurately applied electrodes would give no slow waves at the beginning of an experiment, but during the next 15 minutes there would be a gradual appearance of such waves coincident with the leakage from the electrode (Fig. 1).



FIG. 1.

In this figure the upper tracing shows an electromyogram taken with the electrodes in firm contact with the skin (Table IX, Film 3). The lower tracing was made 11 minutes later with electrodes unchanged except for leakage of zinc sulphate (Table IX, Film 9).

## OBSERVATIONS

By the method described above, five patients were intensively studied; two of these had patellar clonus alone, two had ankle clonus alone, and one had both patellar and ankle clonus. The results of these observations are arranged below in nine tables.

The first patient, H. A., was a boy of 16 with a right-hemiplegia for 13 years. The initial lesion was probably an embolus. During the last two years he had been having epileptiform convulsions. The right leg showed both ankle and patellar clonus and both the right arm and right leg showed extensor weakness. Babinski's sign was present on the right.

The next patient, J. M., was a boy aged eight, admitted March, 1918, for broncho-pneumonia. In June, 1914, he was admitted in a delirium; he was found to have typhoid fever and bilateral ankle clonus without Babinski's sign. In July of that year he had a period of psychotic behavior. In 1916 he had rheumatic fever, and in November, 1917, he came back with choreiform twitchings that were thought to be habit spasms. The clonus was more marked in 1918 than at any time previously observed.

The third patient, R. P., male, aged 40, had phthisis 11 years ago, and eight years ago headaches with loss of sphincter control and weakness of the right leg. For the last five years he had had unconscious attacks. A diagnosis of cerebrospinal syphilis was made on the laboratory findings. There was slight weakness of the right leg with ankle clonus and a positive Babinski.

E. L. was a boy of 14, whose illness began six months ago with drowsiness, unsteady gait, and incontinence. From the physical examination a diagnosis of cerebellar tumor was made and an exploratory operation was performed. The tumor was not located, but great intracranial pressure was relieved. The patellar clonus which was present in the left leg before operation disappeared thereafter.

M. S. was a woman of 40, who had had pain in the arms and legs for five years, with staggering, ataxia, and slight bilateral

spasticity for one year. There was hypertension and the fundi showed extensive arteriosclerosis. Both legs showed patellar clonus, slight ankle clonus, and Babinski.

In arranging these tables, the time at which each record was made is placed in the first column. In the second column is the number of the film. The third column is headed "Periodicity." This signifies the length of time elapsing between the beginning of one contraction and the beginning of the next in a clonus series. It is taken for granted that the appearance of the first wave in the electromyogram of a contraction bears a constant relation to the beginning of the mechanical contraction of the muscle. Simultaneous mechanical and electrical records made by Salomonson<sup>18</sup> show the reliability of this criterion. In recording the periods of the clonic contractions, each period was measured with dividers and read off against the time as registered in fiftieths of a second by the tuning-fork. If the same length of period repeated itself this was indicated by writing the number of times of the repetition above and to the right of the number. For example in Table I,

TABLE I.—ANKLE CLONUS  
(H. A., March 8, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action currents per sec.	Average number of action currents per contraction	Remarks
3.15	1	.18, .15 <sup>1</sup> , .14, .15 <sup>2</sup>	6.6	2	110	2	
3.16	2	.16 <sup>1</sup> , .17, .16 <sup>2</sup> ...	6.2	1.5	110	3	
3.18	3	.16 <sup>1</sup> .....	6.2	3	110	2	
3.18	4	.14 <sup>1</sup> .....	7.1	2.5	120	3	
3.20	5	.15 <sup>1</sup> .....	6.6	2	120	3	
3.21	6	.14 <sup>1</sup> , .15 <sup>2</sup> .....	6.8	2	110	3	

TABLE II.—ANKLE CLONUS  
(H. A., April 27, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action currents per sec.	Average number of action currents per contraction	Remarks
3.16	1	.16 <sup>1</sup> .....	6.2	1.5	130	4	Light steady stimulus.
3.17	2	.18, .17 <sup>1</sup> , .16 <sup>2</sup> , .17, .15.	5.9	2.5	130	5	Same stimulus.
3.22	3	.17, .18 <sup>1</sup> , .14 <sup>2</sup> , .16, .15.	6.0	1.0	145	5	Light steady stimulus.
3.22	3	.23, .18 <sup>1</sup> , .16 <sup>2</sup> , .15.	6.4	2.5	130	6	Sudden increase in stimulus during record.
3.25	4	.17.....	5.8	1.0	160	6	Light steady stimulus.
3.25	4	.20, .19, .17 <sup>1</sup> , .16, .15 <sup>1</sup> , .14, .15, .16, .18, .17.	6.1	3.0	140	6	Sudden increase in stimulus during record.
3.27	5	.18 <sup>1</sup> , .17 <sup>2</sup> , .18.....	5.6	0.7	160	7	Light steady stimulus.
3.28	6	.15 <sup>1</sup> , .14, .15 <sup>2</sup> , .14, .15.....	6.7	2.5	160	5	Strong stimulus.
3.28	7	.16, .15 <sup>1</sup> , .16 <sup>2</sup> .....	6.3	2.0	150	4	Continued strong stimulus.
3.31	8	.17, .16, .14 <sup>1</sup> , .15 <sup>2</sup> .....	6.6	2.5	135	5	Continued strong stimulus.

TABLE III.—ANKLE CLONUS  
(J. M., March 20, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
2.35	1	.16, .14, .12 <sup>11</sup> , .13 <sup>3</sup> , .13, .14 <sup>2</sup> , .13 <sup>3</sup> , .15 <sup>2</sup> , .12 <sup>2</sup> , .15 <sup>3</sup>	7.8	3.	80	2	
2.45	2	.15, .14 <sup>3</sup> , .15, .14 <sup>23</sup>	7.1	1.	100	2	
2.47	3	.14, .13, .14, .12, .14 <sup>2</sup> , .12, .14, .12, .12 <sup>2</sup> , .13, .14,	7.6	2.	150	3.5	A few waves between contractions.
2.47	4	.13 <sup>3</sup> , .12 <sup>2</sup> , .14, .12 <sup>2</sup> , .14, .12.	7.6	1.5	150	3.5	

TABLE IV.—ANKLE CLONUS  
(J. M., April 13, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
3.25	1	.26, .16 <sup>2</sup> , .16 <sup>2</sup> ...	6.	3.5	150	4	Irregular, discontinuous clonus.
3.27	2	.13 <sup>2</sup> , .11, .13 <sup>2</sup> , .14, .13, .14, .13 <sup>2</sup>	7.6	5.	125	3	Clonus regular and continuous.
3.28	3	.13 <sup>10</sup> .....	7.6	6.	125	3	Clonus regular and continuous.
3.29	4	.14, .13 <sup>2</sup> .....	7.6	6.	125	3	Clonus regular and continuous.
3.30	5	.13 <sup>10</sup> .....	7.6	4.5	125	4	Clonus regular and continuous.
3.31	6	.13 <sup>2</sup> , .14, .13 <sup>2</sup> , .12, .14, .13 <sup>2</sup>	7.6	4.	110	2	Clonus regular and continuous.
3.32	7	.13.....	7.6	5.	110	3	Clonus regular and continuous.
3.35	8	.13.....	7.6	3.5	110	3	Clonus regular and continuous.
3.36	9	.11 <sup>10</sup> .....	7.1	3.5	110	3	Clonus regular and continuous.
3.38	10	.13, .15, .13 <sup>2</sup> ....	7.5	4.	110	3	Clonus regular and continuous.
3.39	11	.13.....	7.6	3.5	135	4	Clonus regular and continuous.
3.41	12	.15, .14, .13....	7.1	3.5	135	4	Clonus regular and continuous.
3.44	13	.13, .14 <sup>2</sup> , .15, .13, .15, .14, .15 <sup>2</sup> , .14 <sup>3</sup>	7.1	4.	135	4	Clonus regular and continuous.
3.46	14	.13 <sup>2</sup> , .14, .13 <sup>2</sup> , .14	7.6	3.	135	3	Clonus regular and continuous.
3.48	15	.14 <sup>2</sup> , .13 <sup>2</sup> .....	7.5	3.	135	3	Clonus regular and continuous.
3.50	16	.13 <sup>2</sup> .....	7.6	3.5	135	4	Less continuous, needs a forcible flexion every min. or two to keep it going.
3.54	17	.13.....	7.6	4.	100	3	Patient begins to complain of fatigue.
3.56	18	.13 <sup>2</sup> , .12 <sup>2</sup> ....	7.6	4.	110	4	
3.57	19	.12 <sup>2</sup> , .13 <sup>2</sup> , .13, .12, .13, .12 <sup>2</sup> , .13.	7.9	4.5	135	4	Stronger stimulus.

TABLE V.—ANKLE CLONUS  
(R. P., April 15, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
2.35	1	.21, .18, .16 <sup>4</sup> , .15 <sup>2</sup> , .14 <sup>2</sup> , .16 <sup>2</sup> , .14 <sup>2</sup> , .15 <sup>1</sup> , .15 <sup>2</sup>	6.6	3.5	110	5	
2.36	2	.20, .18, .16 <sup>4</sup> , .15 <sup>2</sup>	6.4	3.5	110	5	Fresh stimulus.
2.39	3	.20 <sup>2</sup> , .16 <sup>2</sup> , .14, .15 <sup>2</sup> , .16, .17 <sup>2</sup> , .15 <sup>10</sup>	6.5	3.	120	6	Fresh stimulus.
2.42	4	.22, .20, .18 <sup>2</sup> , .16 <sup>4</sup> , .15 <sup>10</sup>	6.5	3.	125	5	Fresh stimulus.
2.45	5	.18 <sup>10</sup> .....	5.5	1.5	100	5	Sample out of a 3 min. steady clonus from one stimulus.
2.50	6	.16 <sup>2</sup> .....	6.2	2	150	4	Fresh stimulus at 2.48.
2.55	7	.16, .17 <sup>2</sup> .....	5.9	2	135	4	Sample out of same series.
2.56	8	.17 <sup>11</sup> .....	5.9	1.5	120	3	Sample out of same series.
2.57	9	.17 <sup>11</sup> .....	5.8	2.	100	3	Sample out of same series.
2.58	10	.18 <sup>4</sup> .....	5.5	1.3	150	4	Sample out of same series.
2.58	11	.18, .19 <sup>2</sup> .....	5.3	1.	165	5	Sample out of same series.
2.58	12	.19 <sup>1</sup> .....	5.2	0.7	150	4	Sample out of same series.
2.58	13	.19.....	5.2	0.5	150	4	Sample out of same series.
2.59	14	.16, .15 <sup>2</sup> , .16....	6.5	3.	135	4	Strong fresh stimulus.

N. B. At 2.48 a steady pressure on the ball of the foot was begun and continued without appreciable change until the clonus spontaneously faded away at 2.58<sup>1</sup>. Then a new strong stretch was given to the muscle, starting up a new clonus at 2.59.

No. 5, the periodicity was .15 of a second for 31 consecutive contractions, this is then written .15<sup>31</sup>.

In the next column the records of periodicity are averaged and interpolated into the rate per second of the clonus as a whole. For example, a periodicity of .15 equals a rate of 6.6 per second.

The fifth column gives measurements of the amplitude of the waves recorded on the moving film. These represent the

TABLE VI.—PATELLAR CLONUS  
(H. A., March 8, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
3.35	1	Average .16....	6.2	1.5	150	2.	Two to three contractions only.
3.37	2	Average .16....	6.2	1.5	140	2.	Two to three contractions only.
3.39	3	Average .16....	6.2	2.	120	2.5	Two to three contractions only.
3.41	4	Average .155....	6.4	2.	110	2.	Two to three contractions only.

TABLE VII.—PATELLAR CLONUS  
(E. L., March 16, 1918. Cerebellar Tumor)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
4.00	1	.20, .20, .16.....	5.27	3.	50	1	
4.02	2	.17, .15.....	6.6	1.	75	2	
4.02	3	.17, .15.....	6.4	1.	85	3	
4.05	4	.20.....	3.	3.	45	1	
4.06	5	.19, .17.....	5.7	2.	100	2	
4.08	6	.18, .15.....	6.0	1.	100	3	

TABLE VIII.—PATELLAR CLONUS  
(M. S., March 29, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
3.30	1	.16, .14 <sup>2</sup> , .13 <sup>3</sup> .....	7.1	1.5	75	3	
3.31	2	.14 <sup>2</sup> .....	7.1	3.	60	2	Followed by tetanus for one sec., then stimulus given and followed by tetanus.
3.31	3	.15, .14, .13 <sup>3</sup> , .12 <sup>3</sup> .....	7.6	4.	60	3	After rest of one min. new stimulus, followed by tetanus.
2.32	4	.17, .14, 12 <sup>3</sup> .....	8.1	4.	60	2	Clonus more easily elicited, end of a series recorded.
3.33	5	.13 <sup>15</sup> .....	7.6	2.	75	2	
3.40	6	.13 <sup>6</sup> , .12 <sup>6</sup> .....	8.	3.	75	2	
3.41	7	.13 <sup>6</sup> , .12, .10.....	8.2	3.	60	2	Followed by tetanus at rate of 75.
3.42	8	.12 <sup>7</sup> , .10, .09.....	8.5	4.	55	2	Running into irregular tetanus.
3.42	9	.17, .15, .13, .14, .12 <sup>3</sup> .....	7.7	3.	60	3	

magnified excursions of the galvanometer string, which in turn were caused by the action currents in the contracting muscle. Their quantitative value lies only in the fact that the tension of the string is so arranged that one millivolt causes a deflection of 1. cm., but this is again affected by the resistance of the patient in circuit, so the figures are only valuable for comparison in a series of observations in which the electrodes are left undisturbed. This is the case in each separate table.

In the sixth column is an average estimate of the rate per second of the action-current waves which go to make up the electromyogram of a single clonic contraction. Those small waves which are not considered large enough to represent an action-current are not counted. A factor of uncertainty, therefore, enters into the estimation of these rates and they must be considered as only approximate. In the next column the number of waves which go to make up the myogram of a single contraction are averaged and recorded. Here again it is difficult to decide whether a small excursion of the string is worth counting as a true wave.

TABLE IX.—PATELLAR CLONUS  
(M. A., April 2, 1918)

Time	Number of film	Periodicity	Average rate of clonus per sec.	Average amplitude of waves in mm.	Average rate of action-currents per sec.	Average number of action-currents per contraction	Remarks
3.40	1	.16 <sup>2</sup> , .13.....	6.6	3.	70	2	3 twitches followed by tetanus at rate of 70.
3.40	2	.16, .14, 12 <sup>3</sup> .....	7.5	2.	70	3	Slight tetanus after 4 twitches.
3.46	3	.17, .16, .14 <sup>2</sup> , .13, .12 <sup>3</sup> .....	7.6	2.	70	2	Amplitude in mm., 2-1, 5-2-1, 8-3-1-1, 5-1-2-1, 8-1, 5-1-1.
3.47	4	.16 <sup>2</sup> , .14 <sup>2</sup> , .13, .14, .13.....	7.1	3.	60	2	Followed by tetanus for 1.4 sec. at rate of 50 per sec.
3.48	5	.16 <sup>2</sup> , .14 <sup>2</sup> , .13, .12.....	7.1	3.	50	2	Followed by tetanus for 1.3 sec. at rate of 60 per sec.
3.55	6	.14 <sup>25</sup> .....	7.1	1.5	60	2	Continuous clonus started at 3.53.
3.55	7	.14 <sup>15</sup> .....	7.1	1.	50	1	Same steady clonus.
3.57	8	.16, .14 <sup>2</sup> , .13 <sup>3</sup> .....	7.3	2.	55	2	New stimulus, and new clonus followed by 1.4 sec. of tetanus at rate of 50.
3.57	9	.14, .13 <sup>2</sup> , .14 <sup>2</sup> , .13 <sup>3</sup> .....	7.4	2.	60	2	New stimulus, followed by irregular tetanus for 0.2 sec.

## DISCUSSION

An examination of the above tables brings out several characteristics of clonic contractions. In the first place it will be noticed that the first few periods are longer than the succeeding ones and that it takes some time for the clonus to fall into a steady rhythm (Fig. 5). For example in Table V, Film 4, the first period is .22 seconds and the second is .20, followed by three periods of .18 and four of .16 before the clonus falls into its regular periodicity of .15; this is also shown in the third film of this table, where after a preliminary unsettled series, the contractions finally repeat themselves 160 times at .15 seconds. This seems to be as characteristic of patellar clonus as it is of ankle clonus (see Tables VIII and IX). It also appears that in any series of records the ones toward the end of the experiment are more regular than those at the beginning (see Table IV).

The effect of repeated clonus and of long continued clonus was also studied in relation to fatigue. Other investigators, notably Levi,<sup>12</sup> have stated that fatigue causes an increase in the rate of the clonus. In the present studies such was not found to be the case; in fact the phenomenon seems to be remarkably constant after the steady rate has once been reached. For example in Table IV it is seen that the rate of clonus is six per second at 25 minutes past three, reaching its steady rhythm of 7.6 per second two minutes later. After 21 minutes of continuous and steady clonus the rate is found to be slower, if anything, and at three fifty when the patient complains of fatigue the rate is still 7.6. At three fifty-seven the clonus has been continuous for half an hour and the rate is 7.9, but this is probably due not to fatigue, but to the factor next to be



discussed, namely variation in the strength of stimulus. Patellar clonus seems to be equally unaffected by fatigue: Table IX shows a rate of 7.5, in Film 2, and at the end of 17 minutes of constant clonus the rate is 7.4 contractions per second. In Table V, Films 7 to 13 show a clonus kept up for eight minutes with only one initial flexion of the ankle as a stimulus; the rate is slower at the end than at the beginning. The patient had altogether 24 minutes of clonus and began with a rate of 6.6 and ended with 6.5 per second. Thus it seems that fatigue in itself does not cause an increase in the rate of clonic contraction.

Variation of the strength of stimulus used to excite the clonus does, however, seem to affect the rate. This is well shown in Table V where the long continued clonus drops from a rate of 6.2 per second to 5.2 and then suddenly jumps to 6.5 when a strong fresh stimulus is given (Films 6 to 14). The explanation of this is as follows: at the beginning the assistant who was holding the patient's foot held the gastrocnemius strongly and steadily stretched; after two or three minutes his grip became fatigued and at the end of five minutes he admitted he was feeling tired, so there was without doubt a gradual diminution in the stimulus, corresponding to the fall in rate. When the new forcible flexion is given to the ankle at two fifty-nine the rate immediately increases from 5.2 to 6.5 per second. In Table II there are recorded experiments especially made to demonstrate this point: at first a light steady pressure was kept on the ball of the foot for six minutes, and the rate of the clonus varied between 6.2 and 5.9 per second. Then a sudden increase in stimulus was given and the rate quickened to 6.4. With the relaxation of this pressure it dropped again to 5.6 and when a continued strong stimulus was given the rate stayed for three minutes between 6.3 and 6.7. It is interesting to note in Table II, Films 3 and 4, that a sudden increase, although it quickens the average rate, first causes a few slow periods like the slow onset of an entirely new clonus.

The amplitude of the waves is the only factor that seems to keep pace with the strength of stimulus and the rate of clonus. With a strong stimulus and quick rate the electrical discharge from the muscle causes higher waves to be registered on the electromyogram than when the stimulus is weak and the rate slower. This shows well in Table II and is conspicuous in Table V. Where there is a new strong stimulus applied to the muscle the waves average from 3 to 3.5 mm. in height, but in the long continued clonus (in Films 6 to 13, Table V) a gradual decrease is shown, the last waves being only 0.5 mm. in height, increasing suddenly again to 3 with the new stimulus. Table II shows records of observations where the increased stimulus was applied while the record was being taken. In Film 3 a light steady pressure was being kept up which gave waves with an average height of 0.1 mm. The stimulus was then suddenly increased and the size of the waves immediately became 2.5 mm. In Film 4 this same thing is repeated with an increase of 300 per cent in the amplitude of the waves. Thus with an increased stimulus and quickened rate the electrical discharge seems to increase.

The 6th and 7th columns in the table show little of importance and too few cases were studied to make any general conclusions, but it may be worth noting that in patellar clonus (Tables VI, VII, VIII, IX) the individual contractions are usually made up of only two waves the rate of which average 50 per second, whereas ankle clonus showed about four waves to each contraction with an average rate of 125 per second. This suggests that patellar clonus is a simpler mechanism than ankle clonus, approximating more nearly a series of tendon reflexes. Salomonson<sup>10</sup> says that in true clonus there is but one action-current for each contraction, and that if two or more are found they are to be considered artefacts due to an "interference phenomenon." He believes that such interference arises when the electrodes are wrongly placed on the muscle. The presumption is that the electrodes are so placed that a single action-current is recorded more than once.<sup>10</sup> That groups of action-currents from a single contraction of a clonus series are not due to such an artefact is proved by recording a tendon reflex which shows a single diphasic wave (Fig. 6) and then, with the electrodes unaltered, eliciting a clonus which shows several action-currents to each contraction (Fig. 7).

A correlation of the height of the patient with his rate of clonus indicates that small size and high rate of the clonus go together. H. A. and M. S. were the smallest patients, and their average rate was 7.6, the others averaging 6.5 per second. This falls in line with the observations of Alexander James<sup>11</sup> who states that "the rapidity of ankle clonus is in inverse ratio to the height of the individual."

Most observers who have written on the subject of clonus have tried to differentiate sharply "true clonus" from "voluntary clonus" or "hysterical clonus."<sup>12,13</sup> Since this paper deals with only five cases, all of which are obviously "organic" it might seem irrelevant to take up the discussion of this differentiation, but in one case of patellar clonus (Table VIII) a constant tendency was noticed for the clonus to go over into a tonic cramp-like contraction (Fig. 4). This tonic contraction gives a tetanic series of waves resembling those shown by Salomonson in hysterical clonus and others shown by Gregor and Schilder<sup>8</sup> (Fig. 47), where a voluntary contraction of the quadriceps muscle turns into a typical patellar clonus. The case described in Table VIII is one of spastic paraplegia with no hint of hysterical complication. The other case in this series which showed a tendency toward tetanic contractions complicating the pure clonus, in the case of J. M. (Tables III and IV). His records not only always showed several waves to each contraction, but also an occasional wave or a short tetanus was found between the clonic contractions. The fact that this is the case of post-typhoidal clonus without Babinski's sign makes one wonder if there is a possible "voluntary" component here, especially as the boy stated that he liked to balance his foot so it would jerk, and enjoyed the interest taken in him by the physicians. Because of such facts as these it seems wiser to make no sharp distinction between the "true clonus" of organic origin, and the "pseudo clonus" of hysteria. In the present state of our knowledge it is more reasonable to think of clonus as a slow, rhythmical neuro-

muscular phenomenon which may be more or less complicated by the faster rhythms of the psychobiologically determined "voluntary" contraction.

#### THEORETICAL

There is probably no distinct line between clonic and sustained muscular contraction. Voluntary contraction is sustained, giving a tetanic electromyogram, but certain individuals can voluntarily induce a clonus. It is notable that such a clonus falls into the usual rate of about 7 per second,<sup>1,2,3</sup> but it is less regular than the pathological clonus studied in this paper, and it can only be elicited by people with hyperactive reflexes or after fatigue of the muscles involved.<sup>4</sup> In this connection it is interesting to remember that clonus is found after wasting diseases such as typhoid fever.<sup>5</sup> Then there is the great group of hysterical clonus which resembles the voluntary type. Only one hysterical case has been studied electromyographically,<sup>6</sup> but this one shows a definite tetanic (voluntary) rhythm underlying the clonus. It should be of great interest therefore to study all clonic contractions electromyographically. In this way a new diagnostic criterion might be found between hysterical and organic cases. The question would be what difference one might find in the clonus in states of normal psychobiological integration and in states of hysterical malintegration, when compared with the organic cases. In purely organic clonus there is no sign of electrical activity in the muscle between contractions. It is interesting that in the case of M. S. where the patellar clonus passes over into a tetanic spasm, the rate and the number of action-currents per contraction increases as the spasm comes on, until the tracing becomes that of a continuous contraction (Fig. 4). Illustrations of the opposite condition are shown by Gregor and Schilder<sup>8</sup> (Figs. 47 and 48) where attempts at voluntary contraction of a paretic muscle give electromyograms showing transition from tetanus to clonus.

Most writers on clonus agree with Langelaan<sup>1</sup> who states that clonus is a reflex symptom, or a series of them; and that the stretching which follows a contraction is a new stimulus to the proprioceptors and calls forth another reflex twitch; thus the symptom propagates itself until fatigue or inhibition puts an end to it. If this were the true explanation of clonus we would expect a much shorter periodicity than that which is observed; Snyder<sup>2</sup> found that the reflex time of the knee jerk was about 0.011 seconds. If then clonus was purely a self-propagated proprioceptive reflex we would expect it to have a much higher rate, for in eliciting clonus we keep the muscles stretched, thus stimulating their proprioceptors, which can reflexly cause a contraction in 0.011 of a second; the muscle then relaxes only to find the stretching stimulus still there to set up another contraction. The fact that the average periodicity is 0.15 seconds when the reflex time is only 0.011 must be explained.

There seem to be three theoretical possibilities. First, it may be that the relaxation time of the muscle takes up 0.1 of a second or more. Secondly, a summation of stimuli through

the proprioceptors may be necessary to cause the next contraction. And lastly central inhibition may play a rôle. The first two possibilities should be studied experimentally. For the last there is some clinical evidence already; evidence for the existence of some energy constantly tending to excite muscular contraction, but normally held in check by inhibition. Removal of this inhibition by decerebration, by central lesion, or positive motor effort, causes more or less permanent muscular contraction. There seem to be all degrees, from slight spasticity to permanent contracture, but the interesting point is that whatever the cause of heightened muscular tone may be, the rate of the clonus (or of the tremor in such diseases as paralysis agitans) falls always into approximately the same rhythm.

Piper, Salomonson, Gregor and Schilder speak of "Innerervationsimpulse" when referring to action-currents in muscles, taking for granted that each action-current represents a single nerve impulse. This theory is not supported by the more recent investigations of Forbes and Rappleye<sup>3</sup> who have shown that warming and cooling the muscle changes the rate of its action-currents. They conclude (p. 254) that "the rhythm observed in muscle response is not the rhythm of motor nerve impulses, but is dependent, as Buchanan maintains, on the condition of the muscle." Action-currents therefore, must be looked upon as electrical concomitants of neuromuscular activity, their rate and character being controlled not only by the rate of the nerve impulse, but also by the physiological state of the muscle itself.

In closing I wish to express my appreciation to Messrs. L. S. Chapman and P. R. Holtz for their help in making the galvanometric records. I also wish to thank Dr. Meyer for his interest in the work, and the other physicians of the hospital who gave me the opportunity to study their cases.

#### CONCLUSIONS

- (1) Electromyography is a more accurate and more easily applied method for the study of muscular phenomena than those formerly applied to clinical observation.
- (2) Clonus gives a characteristic electromyogram.
- (3) Fatigue does not affect the rate of clonus.
- (4) Increased stimulus increases the rate of clonus and the size of the electromyographic waves, but does not change the rate of the action-currents.
- (5) The number of action-currents per contraction varies with the type of the clonus.

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#### DESCRIPTION OF PLATE

FIG. 2.—Ankle clonus; electromyogram from gastrocnemius muscle. (See Table II, Film 2.)

FIG. 3.—Patellar clonus; from rectus femoris muscle. (See Table VIII, Film 9.)

FIG. 4.—Patellar clonus ending in spasm, electromyogram showing the transition from periodic to tetanic waves. (See Table IX, Film 5.)

FIG. 5.—Patellar clonus, low speed film, showing that the periods are longer at the beginning, and quickly shorten to a more constant periodicity, in this case the periods are: .17, .14, .12". (See Table VIII, Film 4.)

FIG. 6.—Patellar reflex, showing single diphasic wave.

FIG. 7.—Patellar clonus, record taken immediately after Fig. 6 without shifting electrodes. Clonus set up by steady pressure on patella. Note that each contraction has several action-currents.

In each case the upper tracing is the shadow of the tuning-fork vibrating at 50 D. V. per second, and the lower is the electromyogram.

## LAVOISIER AND THE HISTORY OF THE PHYSIOLOGY OF RESPIRATION AND METABOLISM. CONTEMPORARY VIEWS OF LIFE PROCESSES

By JOHN C. HEMMETER, M. D., PHIL. D.

Antoine Laurent Lavoisier, the son of a rich merchant, was born August 26, 1743, in Paris. Little can be ascertained concerning the degree of culture and the intellectual status of his parents. Alphonse de Candolle in his "History of Science and of Scientific Men" gives no reference to the genealogy. De Candolle, a member of the Academy of Sciences, Paris, would have been in a position to ascertain the truth on this point. Galton and Wilhelm Ostwald, who endeavored to trace the ancestry of Lavoisier. Prof. Edouard Grimoux (Lavoisier) gives the genealogy of this famous chemist on the paternal side back to 1620 (see Grimoux, pp. 325-331). There is no one in the list of ancestors from whom it could be claimed that Lavoisier received his great genius by hereditary transmission. The studies in the hereditary transmission of genius by Galton, de Candolle, Ostwald, and Raibmayr, find no family basis for their theories in the genealogy of Lavoisier. He was educated at the Collège Mazarin, his studies being directed towards the study of law. He soon developed a preference for natural science. He was instructed in astronomy by La Caille, in chemistry by Rouelle, and in botany by Bernard de Jussieu.

The earliest of Lavoisier's inquiries was an "Analysis of Gypsum," presented to the Academy of Sciences in 1765, and published in the collection of "Mémoires de Divers Savants," 1768. His next work of importance was a paper on "The Practical Illumination of the Streets of Paris," for which a prize had been offered by the Chief of Police, M. de Sartine. This prize was not awarded to Lavoisier, but his suggestions were of such importance that the King directed that a gold medal be bestowed upon the young author at the public sitting of the Academy in April, 1766. Two years later, at the age of 25, he was admitted to the French Academy of Sciences.

He sought and received appointment as "Fermier Général," a position unique in the French Government of that day. The closest approximation to it appears to be a sub-collector in the

Department of Agriculture, controlling mainly the revenues (tax on salts, state sales on tobacco, etc.).

In this position he showed himself a skilful administrator. In 1776 Turgot placed him at the head of the Régie des Salpêtres, where he introduced many improvements into the manufacture of gunpowder. From 1778 to 1785 he gave attention to agriculture and contributed many valuable suggestions to the science of husbandry. In 1787 he was elected to the Provincial Assembly of Orléans. In 1788 he became one of the trustees of the Bank of Discount and in 1789 he was an assistant deputy to the Constituent Assembly. In 1790 he was a member of the Commission on Weights and Measures and developed great interest in the preparation of a new decimal system. In 1791, as one of the commissioners of the Treasury, he published an essay "De la Richesse Nationale de France," in which he presented a plan for the collection of taxes. It was said by the Minister of Public Instruction (who published all of his works from 1864 to 1893) that this essay was a forerunner of a complete treatise on this important subject, and entitles him to a high rank among political economists.

In the "Œuvres de Lavoisier," "publiées par les Soins de son Excellence, le Ministre de l'Instruction Publique," 1864-1893, the incontrovertible evidence of great gift of exposition, power of logic and unparalleled acuteness is manifested. These works embody the principles out of which chemical science was to be renovated. His greatest work is his "Traité Élémentaire de Chimie," 2 vols., 1789, in which the basis of modern chemistry is laid. In 1777 he published in the "Mémoires of the Academy of Sciences" an essay, "Du Principe Constitutif de la Chaleur," which marks the transition of his attention to the application of chemistry to physiology. Some of the more specific experimentations on physiologic chemistry will be explained at a later stage. By this time, the revolutionary movement against Louis XVI and





ANTOINE LAURENT LAVOISIER. BORN AUGUST 26, 1743. EXECUTED DURING THE FRENCH REVOLUTION, MAY 8, 1794.



Marie Antoinette was in full progress. He was collecting all his writings with the ultimate view of remodelling them into a single work, when the course of the revolutionary events brought him to a premature end. Dupin, a member of the Convention, having on May 2, 1794, introduced a formal accusation against all the farmers of the public revenue (*Fermier Général*) Lavoisier delivered himself up and was imprisoned. On the 6th he was involved in the general sentence of death against the corporation to which he belonged, and two days later he was guillotined. His essays were collected and published by his widow (who afterward married Count Rumford), under the title of "*Mémoires de Physique de et Chimie*," in two volumes. A complete edition of his works has been published under the supervision of the Minister of Instruction at the expense of the government (4 vols., Paris, 1864-1868).

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During the years which followed her husband's death, Mme. Lavoisier was preoccupied with numerous affairs of a personal nature. These finished, she hastened to complete the task undertaken by her husband and arrested by his death.

In 1792 Lavoisier had conceived the idea of publishing his principal data, and of collecting the works of the other scientists who had contributed to the making of modern chemistry a greater science. This work was to be compiled in eight volumes. The first imprint was made at the end of April, 1793. Lavoisier, with the help of Seguin, did the proof-reading during his detention. When he died, the first two volumes were almost entirely printed, as well as a few pages of the fourth. The fourth year (1796), Mme. Lavoisier had a meeting with Seguin in order that these works might appear before the public and asked him to edit a preface, but she required that it should brand the men guilty of Lavoisier's death. Seguin refused. "To denounce those who had him condemned or who let him perish does not strike my fancy and, on the other hand, would diminish the horror that the event has left in all hearts. There are certain things more difficult to tell than to have told by the consciences of those to whom they were presented. Oftentimes they acquire more force from these witnesses. If you do not agree with me, you may have your own views printed; in your own words they would acquire a more convincing tone, proceeding directly from you." (Letter from Seguin dated July 18, 1796.) At the same time, he sent with this letter a sample of a preface which could never have pleased Mme. Lavoisier, for he attributed to himself an equal part with Lavoisier in the project of the publication of the works, saying, for example, "The plan *we* had thought about, the design *we* were meditating," etc.

Mme. Lavoisier gave up the project temporarily but took it up a few years later. She edited an introduction herself, in which she explained the conditions under which Lavoisier had undertaken this work. We publish it in its entirety:

In 1792, Lavoisier conceived the idea of making a collection of all his works that had been read at the Academy during the 20 preceding years. In a way, it was the making of modern chemical history.

To make this history more interesting and more complete, he had proposed to add the works of those who, having adopted his system, had made experiments in his behalf.

This collection was to number about eight volumes.

Europe knows why they were never completed.

Almost all of the first, all of the second, a few pages of the fourth, have been finished.

Many scientists have desired to see those published. We hesitated a long time. It is difficult not to feel a certain fear when it comes to publishing the unfinished works of a man who justly enjoys a great reputation. It is when we have lost him that friendship must become impartial and show only what might add to the glory of a cherished and honored name.

We would have persisted; and their fragments would never have appeared if they had not contained (page 78 of the second volume) one of Lavoisier's ideas which claims, from the accompanying proofs, that he was the founder of the new chemical theory.

Thus it becomes a duty to confirm the views which scientists have expressed in regard to this question.

We beg their indulgence for the mistakes that may have been made in some other part of this collection.

They will surely grant this request when they learn that most of the proofs were reviewed in the author's last moments, and that, although he did not ignore the fact that his murder was premeditated, M. Lavoisier, calm and courageous, compiling a work which he thought would be useful to science, gave a memorable example of the serenity which intellectual purity and virtue can produce in the most unfortunate hours.

The two volumes of the "Treatise on Chemistry," published in 1805, were not placed on sale, but given to all of the eminent men of this period. Cuvier thanked Mme. Lavoisier in the following words for her gift of the work to the class in sciences at the Institute:

Madame, the class requests me to thank you for the work which you have so kindly given them, precious to all as well as to each one. Allow me to offer the testimony of my gratitude. All the friends of science are indebted to you for your heroic determination to publish this collection, and to publish it as it had been originally planned, a sad memorial of your loss as well as theirs. These incomplete volumes, these unfinished utterances, make a profound impression. What truth, it seems, we were about to learn in a book which began with so many truths so beautiful and so new, and yet how we feel the horror of the crime renewed in all its force, a crime which has afflicted humanity perhaps for centuries!

Historical comments upon scientific researches are subject to manifold errors. The language of science has undergone so many changes in the course of time, that it is often difficult to grasp the real ideas of an author, even though he writes in our own mother tongue. The more distant his views may be from ours, the more readily are we tempted to form erroneous impressions of his meaning. Indefinite announcements often have been considered as discoveries, which were actually and really only made at a later period. Deficiency of exact sci-



tific knowledge occasionally produces erroneous ideas, which may engraft themselves as truths, by repetition; whereas, if such false ideas were not permitted to take hold of us, our thoughts would be led in another, safer and surer, direction.

No one can become independent of the influence which intellectual activity exerts upon seemingly wholly different fields of contemporary knowledge. Sensational discoveries are at once applied to other branches of science, and like newly issued coins, no matter how limited in value, are overestimated, until further investigation reveals their inferiority.

All this is true of our own time, and if this is so, we may conclude that much which is regarded as genuine coin to-day will be cast aside as spurious by those who come after us. We have a right to hope, however, that as methods of investigation improve and the true value of the acquisition of knowledge increases, there will be less need for elimination in the future. It is precisely to this matter of advance in the methods of experimentation that I wish to call your attention.

I will not take you back into remote times, only a period of 123 years, and review the ideas which engaged the minds of men of that time on the remarkable phenomena of nature. The great question of the difference between the organic and the inorganic world has from ages immemorial been uppermost in the mind of the scientist.

The status of the natural sciences about the middle of the 18th century was by no means a low one. Bacon in a most exemplary manner had defined the fundamental principles of inductive research; and eminent investigators, such as Galileo, Kepler and Newton, by observation and experiment, had established the most important fundamental laws of physics. In the science of man, the advances in anatomy by Vesalius were enhanced by the discovery of the circulation of the blood by Wm. Harvey, and placed upon a firm basis by the work of Haller. Chemistry enjoyed special growth about this time and we shall consider this with greater detail since the activity of Lavoisier is most intimately associated with its development.

In my biography of Haller (JOHNS HOPKINS HOSPITAL BULLETIN, Vol. XIX, March, 1908) I referred occasionally to one who stood at the head of science of that epoch—Geo. Ernst Stahl—one of the foremost minds of his time, whose views not only controlled chemistry, but general medicine as well. Stahl's influence rested upon the fact that he understood how to gather together into one general viewpoint the various natural sciences of his time. We may at this day reject as false his so-called "phlogiston" and "anima" theories, but we must not forget that both had a great value, because the sum total of the then existing knowledge was embraced in a unity in Stahl's doctrines which thereby accomplished what we now expect from each single theory.

When Lavoisier began his career, the phlogiston theory was universally recognized and he too was fully in accord with it, for he included the hypothetical heat substance and light substance in his table of chemical elements. (See Wilhelm Ostwald: "Die Forderung des Tages," p. 18.) Looking upon his researches from their beginning, we can trace, step by step, the method by which he at first hesitatingly, then with ever-increasing certainty, began to doubt, and with conviction

passion for new truths, began to criticize and finally demonstrated the untenableness of the hypotheses of Stahl.

Lavoisier did not bring about this advance by his own exclusive efforts, but by the adroit use of the discoveries of his contemporaries. He is, however, clearly entitled to the honor of having originally applied the measures adopted at a later time in chemical processes and by which he really is to be looked upon as the founder of modern chemistry. Boruttau in Neuberger and Pagel's "Handbuch der Geschichte d. Medizin" calls him the "*Vater der modernen Chemie*."

It is not my intention to review in general all the work of this great man. His achievements proper have been detailed sufficiently often, and for lack of proper time I must refer you to the excellent statements of Grimaux, Neuberger and Pagel (l. c.), Kopp, Ladenburg, E. V. Meyer, Würtz, Lord Brougham, and others. One more point I wish to dwell upon, namely: Lavoisier's demonstration of the *established fact that in chemical processes the amount of matter present is neither increased nor diminished*. This fact, first demonstrated by him in a number of experiments, has since become an *established law, the law of immutability of the matter present*. This law applies not only to processes pertaining to inorganic, but also to organic substances and for all interchanges between these and the outside world. Clear as this is to us now, many statements appeared in the text-books during that century contradicting these theories. According to Vauquelin, for example, calcium is generated in the body of the chicken, because he thought he had discovered that more of this substance was excreted than had been ingested by this animal.

The prominent position which Lavoisier holds in the history of physiology is due to his series of researches in special physiologic chemistry, overthrowing the then existing "*vitalism*" of Stahl as in his chemie investigations he destroyed the "*phlogiston*" doctrine.

The subject of fire and heat has attracted the attention of naturalists from time immemorial. Stahl (1660-1734) explained these phenomena by affirming that "heat matter" was contained in all combustible bodies and was made to appear when such bodies were burned. He called this heat matter "*phlogiston*." Lavoisier, however, showed that the burning of combustible substances—coal for example—depended upon the oxygen contained in the air, an element recently discovered by Priestley (1774) and almost simultaneously by Scheele (1775); also that animal respiration is a process of combustion by which this O combines with the other bodily constituents of the animal, and that by this union with O the expired air contains CO<sub>2</sub> and H<sub>2</sub>O, as already previously demonstrated by Black. True to his theories, and not satisfied with his general proofs of these processes, he and Seguin made numerous examinations of the expiratory air of man and animals, and thus added largely to the furtherance of our knowledge of the phenomena of life. Since then his experiments have often been repeated by almost identical methods.

When we consider that Lavoisier was the originator of the practical methods, even of elementary organic analyses in use at the present time, and that by the same he demonstrated the composition of the organic substance as made up of C, H, O,

and the occasional presence of N, we can realize that he laid the foundation of physiological chemistry in such completeness that his successors could merely build upon the structure he had created, but for many years could not contribute any material additions. We have, however, not exhausted the subject of the value of Lavoisier's discoveries. A far greater contribution will have to be considered—the explanation of *animal heat*.

Physiologists of all times have endeavored to expound the phenomena that certain members of the animal world, all mammals and birds, during life, possess a temperature far exceeding that of their surrounding conditions, and unchangeable under the most diverse circumstances. Some assumed that this body heat is inborn in the animal, with about as much reason as that of the animists, who held that it was a product of the soul or of the *life-spirit*, to which all the mysterious problems of life were attributed. An exception to this was made by the so-called iatro-mathematicians, who accounted for body heat by the friction of the blood circulating in the vessels, or compared it to heat generated during putrefaction and fermentation, which may have come near enough to truth without leading to further conclusions, as no one understood the cause of heat formation in those conditions. After Lavoisier, however, correctly interpreted the process of combustion and recognized the similarity of the physiologic chemistry of respiration to combustion, he was naturally led to view the heat formation of animals from the same standpoint.

The adherents of the phlogiston theory looked upon fire or heat as a matter, or element, like their other "elements"—earth, water and air. During combustion and the so-called "calcination" of the metals, "phlogiston" and with it heat was liberated from the burning bodies. Later when combustible H gas was discovered by Cavendish in 1781, many claimed that this was phlogiston proper, or air highly charged with it; whilst, on the other hand, O was thought to be "dephlogisticated" air. These views took such a firm hold on the chemists of that time, that even the well-known fact of increase in weight during calcination, which Lavoisier showed to be due to absorption of O, did not convince them to the contrary, but they rather added a new hypothesis, namely, that phlogiston possessed a "negative weight." CO<sub>2</sub> was discovered by Black in 1757. N by Rutherford in 1772. O by Priestley, 1774; Scheele, 1775; Lavoisier, 1775; Hirn, 1781.

When, however, Lavoisier had become thoroughly convinced of the untenability of the phlogiston theory, he could not but draw into his investigations the heat that was generated during all processes of combustion. Like other naturalists he still supposed this heat was some form of matter, although unweighable; an imponderable substance, such as magnetism, electricity and the like. Although this conception has been given up, the method of estimating heat, first demonstrated by Laplace and later utilized by Lavoisier to measure the heat produced by animals, still holds good to-day. And since they compared the heat given off with the expired CO<sub>2</sub> they believed from their experiments that animal heat was a result of combustion going on in the body.

For the first time a firm foundation was laid for the understanding of the fundamental phenomena of animal life. The conceptions of the times were like this: The animal body is in the main composed of matter consisting of C, H, O and N. These elements may, however, take up a larger amount of O than they originally contain; therefore, they unite with the O transmitted by respiration whereby CO<sub>2</sub>, H<sub>2</sub>O and certain nitrogenous bodies are formed and are expelled. By this combustion, heat is generated. Now since a portion of the body substance is removed by excretion, the animal loses in weight. This loss is replenished by the food substances, which are composed of the same elements as the animal body itself, so that with proper intake it will continue its existence for a longer period of time. Life process, in many respects, may be likened to the burning of a lamp; in fact, the materials fed to the latter are identical in composition with the food-stuffs.

These are the principal features of the theories advanced by Lavoisier as a result of his physiological investigation, of such striking simplicity and so amply verified by experiments, one would think that the physiologists of his time would eagerly seize them in order to emerge from the difficulties of understanding the phenomena of life. This was by no means the case, and by study of the literature of that period, we shall endeavor to ascertain the reasons therefor.

Although the reign of the phlogiston theory fell by the blows given by the chemical discoveries of Lavoisier, and all reputable chemists sided with the antiphlogistic theory (as it was then termed in contradiction), still neither physiologists nor philosophers, and least of all the chemists, in reflecting upon the phenomena of life, could rid themselves of the opinion that these phenomena were of an entirely different order from those of inorganic nature, and, although similar in character in some details, must arise from some special power or cause of their own. Lavoisier's chemical theory of respiration and heat production gave no answer to the difficult question what life really is, and no satisfactory answer to the question, what the hypothetic cause of animal heat was, whether, according to the hypothesis of Paracelsus, it might be called *archeus*, or, according to Stahl, it was the *anima*, the soul or vital force. The thinkers of the time inclined to the same views upon which the alchemists based their theories. Like those who searched for a matter, the "*quinta essentia*," which should convert all metals into gold, the possessor of which would become wise and immortal, so did these investigators search for a term or formula by which all enigmas would be solved and all secrets disclosed. And since no such formula was discovered, shorter terms, at least, were adopted for the restricted field of phenomena. As to the phenomena of life in particular, some attributed them to vital force itself, others to the "*nixus formativus*" of Blumenbach, and yet others to the "irritability" theory of Haller. The most generally adopted view was that of Stahl, who looked upon the characteristic of life substance as the power of resistance against putrefaction.\*

\* "*Vita nihil aliud est formaliter, quam conservatio corporis in mixtione quadam corruptibili, sed sine omni corruptionis actualis eventu.*"

In the fortifying and dissemination of these views much was done by a man whose achievements in other fields of scientific labor deserve our fullest recognition, Xavier Bichat. He is the creator of general anatomy, from which our present histology or the finer study of the tissues became developed. As a true adherent to the *vitalistic* school, chiefly upheld by the University of Montpellier, he extensively spread this study in his works and for a long time held unlimited sway. His definition of life, "La vie est l'ensemble des fonctions qui résistent à la mort" ("Life consists in the main of the functions which resist death"), is fundamentally nothing but a transcription of Stahl's theory. Bichat's great influence, especially in his own country, is to be attributed to his elegant and attractive manner of discourse, rather than to the inherent value of his teachings.

According to Bichat, we have to distinguish between two kinds of bodies, animate and inanimate, and two series of phenomena, physical and physiological. The first are produced by physical causes, weight, electricity, etc., the other by physiological, the capacity for extension, contractility and irritability. The first act according to unchangeable laws, the latter do not. It is therefore impossible to determine the physiological phenomena by the same methods of physical investigation, and he speaks with some contempt of these efforts, clearly alluding to Lavoisier, without, however, mentioning his name.

To this inward impulse for knowledge and the search for an uppermost principle, two especial contemporaneous products of thought came to aid, which again are closely interwoven, *natural philosophy* and *galvanism*. Natural philosophy, in the form given to it by Schelling (system of 1797), had exerted the greatest influence in the development of the natural sciences, especially in Germany. This influence has been much dwelt upon and has met with severe condemnation, which its later exorcisances justly deserved. A complete estimate of natural philosophy as conceived by Schelling cannot here be undertaken and only the effects of these theories on the conception of the process of life will be pointed out. Schelling places the highest law of nature upon a trinity: everything springs from two opposite activities, united together by a third—(I) the expanding, (II) the retarding activity and (III) the weight—which are to be looked upon as the equivalent of matter, whereas the latter represents the product of the three activities. Nature as a product of the active substance proper is represented as inorganic, organic and cosmic. The activity of nature is retarded in the first, productivity is continued in the second, whilst in the cosmic the co-existence of the first two is brought about. In *inorganic* nature, the trinity is exhibited as magnetism, electricity and chemism; in the *organic*, as sensibility, irritability and reproduction; in the *cosmos*, as light, weight (gravitation) and accelerating and retarding force. All organization proceeds from light, which corresponds to world soul, and tends to the production of intelligence. This, however, is attained only in man, the *microcosm*, who also encompasses everything contained in the *macrocosm*, and therefore can produce everything in the form of thought. The

laws of nature must therefore be regulated by the laws of consciousness, and the one may be deduced from the other. See Schelling's view of nature in "History of European Thought in the 19th Century," by John Theodore Merz, Vol. III, p. 556, etc.

The broad and sympathetic interpretation of John T. Merz can make even the obscure speculations of Schelling appear interesting to a modern physiologist.

In this system, of which no adequate conception can be made from these preceding sentences, analogies play an important rôle. They must often take the place of proof. The influence of galvanism with its polarities is unmistakable. This very fact induced physiologists of that time to take sides with that system. Galvani's discovery of the wonderful effects of the constant current upon muscles and nerves had made a powerful impression. In galvanism the key was sought and found for the phenomena in nerve and muscle activity and later that of life phenomena. Thus, for example, Prochaska, the Viennese physiologist, in the preface to the renewed edition of his text-book in 1820, states that "*life processes and galvanism rest on the same foundations*," and boasts that the new edition was worked according to this principle, as is seen from the title on page 47 of the chapter on this subject, "*Life as a matter of fact proceeds from the laws of electrical processes*." The number of treatises on the subject of galvanism which appeared at that time is too great to enumerate. I will mention only one, because it is interesting on account of its author—Alex. v. Humboldt's work in two volumes, on irritability of muscle and nerve fiber.

Looking over the text-books of that time, we find everywhere traces of these influences and I shall refer to one in particular because it is typical. Geo. Friedr. Hildebrandt, professor of physics and chemistry at Erlangen, is best known by his text-book on anatomy, which appeared in 1789-1792, and was revised in 1830-1832 by E. H. Weber, the same who discovered the inhibitory action of the vagus on the heart in 1845. He is also the author of text-books on chemistry and natural sciences, and his work on physiology, first published in 1796, was republished by his son-in-law, Hohnbaum, in its sixth edition, from manuscripts he had left at the time of his death. Hildebrandt was a sober, industrious worker with astonishingly broad knowledge. He constantly emphasized the importance of experience as against construction from general and convincing hypotheses. In spite of this, especially in his later edition, "polar matter" and "*Grundkräfte*" ("fundamental forces") play an important rôle with him. All matter is grounded on the union of the dual expansible and attractive force. These may also become dissociated, in which case the superfluous will act also upon distant bodies. By this are generated magnetism, electricity, chemical processes and the higher stage, life. For this reason both forces act during life: the *expansible* more so, which appears as light in its free state, but in the living body as *life-turgor* (I gather the impression from Hildebrandt's book that he uses the word *turgor*—from *turgescere*, to swell—as modern physiologists use the word "tonus" or tonic) by which development and growth are



brought about. The *attractive* force, however, is not missing, for from it we have the chemical and mechanical processes.

All this may impress one as a play of words. The same is felt by the author, for he continues immediately after his exposition, as follows: "However, we must not conclude after these explanations that we have lifted the veil of the secret of life, which covers that of the entire creation. All is hypothesis that our physiologists have to offer as to the problem of life, and what the older physiologists said about the same, although more recent investigations have penetrated deeper into the mysteries of nature than was possible with the former." The "deeper penetration" refers to Schelling's natural philosophy and as pictured in the mind of Hildebrandt. However, on the whole, he was not inclined to be speculative and had he appeared in the middle of the 19th century, he would have been looked upon as a rank "materialist."

According to him, nature yields only matter, coarse and fine; by the latter he means imponderable, and it has been so designated from that time to the present. By admixture only of these, all phenomena are, and even life is, produced, not as Reil thought by mixture and form, because the latter is contained in the former, being generated by it.

Reil plays the same rôle for vitalism in Germany as Bichat does in France. He founded the "Archives for Physiology," the first volume appearing in 1796 and containing an extensive treatise on the life energy—"Lebenskraft." According to Reil, there are two series of phenomena: (1) Matter and (2) conceptions (opinions). The phenomena of the living body, in so far as they are not due to the conceptions or opinions, have their foundation in animal matter, in the mixture of matter (admixture) and form, that is, chemical combination. He holds that "energy" is the relation of these phenomena to the properties of matter by which they are generated; consequently, "vital energy" results from material circumstances, but is not perceptible to the senses owing to the incomplete state of chemistry and lack of knowledge as to the nature of the so-called "imponderables." Therefore, every organ, every tissue, possesses its own vital power due to its chemico-composition and form. In his endeavor more closely to confirm these properties, Reil then also resorts to defining life phenomena as "potential galvanic processes."

The unfruitfulness of all these speculations, especially their outgrowths, which natural philosophy of that period carried on, was that no special research for facts was made in single and individual problems or fields of research, but the thinkers aimed to trace everything from the "uppermost principle" by deduction and intuition. This was the reason for naturalists of better mind entirely to turn away from these theories. In justice, however, we must admit that philosophic ideals had a stimulating effect on many branches of our sciences, especially embryology and comparative anatomy. The fundamental phenomena of animal life, however—namely, Lavoisier's discovery of continuous oxidation of its component parts, and the metabolism accompanying it—remained unsolved. Even such an erudite man as Herman Lotze, physician and philosopher, could not arrive at a clear understanding, and as late as 1851,

in his "General Physiology," he makes an unsuccessful attempt to explain it teleologically, by the assumption that the body by its continual changes in its component parts is rendered more able to resist outside disturbance. Likewise, the eminent Johannes Müller, who embraced so masterfully the entire physiologic knowledge as it was understood up to his time, could not arrive at a correct conception regarding this fundamental question.

Lotze was one of the first scientifically to attack vitalism, without, however, making much impression. He strove to justify the teleological viewpoint in a philosophical way. It appears possible that this viewpoint can be directly deduced from the premises of the old natural philosophy, but his arguments are defective. As a fact, there undoubtedly is a definite conformity to purpose and to arrangement in organic nature; however, it is not restricted to organic nature, but belongs to nature in its entirety, and to understand the details it is often necessary to ask what purpose or object is fulfilled by this or that part of the whole organization. We must, however, be very careful not to overlook the fact that we are introducing a conception thereby, which can have a meaning only from the standpoint of an individual who acts with a precise and conscious purpose; objects of nature, however, present themselves to our investigation as concrete objects. It is not necessary further to expound to this audience Darwin's theory as to how living things develop conformably to purpose.

Chemists are justified in feeling an inspiring pride in the contributions their historic fellow-workers have made to physiology, for the next impetus to revivifying physiology came from J. Liebig.

After having materially improved upon the elementary organic analysis created by Lavoisier, he applied his vast knowledge of chemistry to the study of conditions of nutrition in animals and plants. What he taught in this field is in part less the result of experimental investigation than it is deductive conclusion from basic chemico principles. Much of this has been found to be erroneous. Nevertheless, he is entitled to the credit of having spurred on the scientific investigation of metabolism and to have again pointed out to physiologists the important significance of Lavoisier's fundamental doctrines.

Before proceeding further, we must go back to the end of the 18th century and consider the life process in plants, especially their nutrition. As early as 1779, Priestley discovered that plants were capable of converting the atmosphere of confined spaces, which had proven fatal to animals, in such a way that the air again became respirable. In the same year Ingen-Housz showed that only the green parts of the plant were capable of doing this, and then only in the light, that they absorb  $\text{CO}_2$  and exhale  $\text{O}_2$ , that contrariwise in the dark all plants, and those not of green color always, take up  $\text{O}_2$  and give off  $\text{CO}_2$  just like animals. In the further course of this research he established his theory of plant nutrition. He showed that the carbon which the plant stores up during its growth could not come from the soil, but from the carbonic acid of the atmosphere, the oxygen of which is liberated whilst the carbon combines with the elements contained in the water

(and in part with N) taken up by the roots. His discoveries were in the main confirmed by Senebier, who, however, erroneously supposed that carbonic acid was absorbed by the roots. Th. de Saussure studied these processes more accurately and demonstrated that larger amounts of  $\text{CO}_2$  act favorably upon the plant only in strong light (atmospheric air contains but a small quantity of  $\text{CO}_2$ , only 3 to 4 parts in 10,000); that the increase in the weight of the plant is greater than the amount of carbon taken up, because water and salts, the latter in slight quantity only, are absorbed from the soil; that respiration goes alongside with the decomposition of  $\text{CO}_2$  even in the light; that the plant does not absorb N from the air but from the soil, which was later positively confirmed by Boussingault. If we add to this that Maret in 1834 showed that fungi, which lacking in green coloring matter (chlorophyll) take up O and give off  $\text{CO}_2$ , we shall have summarized what Liebig found already established when he entered the field of investigation of plant nutrition.

In spite of these achievements the practical agriculturists, as well as the theorists, clung to the theory that the so-called "*humus*" was necessary for plant development and that the plant derived its whole sustenance and carbon from it. Liebig had completely set aside this "*humus*" (soil) theory and thereby gave to agriculture a rational principle of fertilizing. For us it is of greater importance firmly to settle the so-called circulation of matter in the organic nature. The plant takes  $\text{CO}_2$  from the air, N and  $\text{H}_2\text{O}$  from the soil and forms organic bodies from these substances, which with the addition of a small amount of salts make up the greater portion of the plant. Plants serve as a nourishment to animals, directly to herbivora and indirectly to such carnivora as thrive upon herbivora. In these the C is in part again converted into  $\text{CO}_2$ , and H into  $\text{H}_2\text{O}$ , whilst another portion of these bodies is excreted in combination with N, in a form which in turn readily passes over into  $\text{NH}_4$  and as such is again taken up by the plant. The same products result from putrefaction in both animal and vegetable bodies. Therefore, the fundamental law of *conservation of matter* discovered by Lavoisier on a small scale for chemical processes has been shown to take place identically in the larger interchanges of matter transformations throughout the earth.

In spite of the emphasizing of the chemical standpoint in the consideration of life phenomena, Liebig held that these depended upon a special vital power, which, however, did not set aside chemical influences, but directed the same and held them in check. This general view held by all writers of that time may be traced back to the apparent difficulty in understanding how the living body maintains its composition, whereas immediately after death it becomes dissociated by decomposition or putrefaction. In reality this difficulty does not exist, since the living body is constantly being attacked and partially consumed, with this difference, that during life the substances lost are at once replaced.

Whilst up to this time the chemical view was exclusively held with regard to these discoveries, physical views came to the foreground in the middle of the last century, incited by Helmholtz

through his epoch-making publication, "On the Conservation of Energy." From this viewpoint du Bois-Reymond in his celebrated introduction to his "Researches on Animal Electricity" explained the untenability of the doctrine of the *vital force* and emphasized particularly that the phenomena of life cannot be differentiated from the inorganic world and that it is the province of science to make plain both series of phenomena upon identical principles in so far as it is scientifically possible.

We have seen above in what manner Laplace and Lavoisier attempted to explain that animal heat was slowly produced by slow combustion going on within the body. But their experiments and calculations were not exact enough to settle such an important question. Dulong and Despretz in 1822 sought to determine the matter by new experiments urged on by the prize offered by the Academy of Paris. They arrived at very incomplete results, for according to Dulong only 75 per cent and Despretz 80 per cent of animal heat is generated by combustion. How the balance of 20 and 25 per cent was produced remained a complete mystery. So that it is not to be wondered at, that in the many writings on physiology it was always suggested to that animal heat was something especial, that it was caused by the nervous system, or by vital force, and that, therefore, no constant relationship was necessary between the heat produced and that of the material burned.

Still later, it was shown that neither the experiments of Dulong nor of Despretz nor their methods of calculations offer a binding conclusion and that we have sufficiently concordant estimations in the results of experiments and calculations of caloric values of the nourishment taken, provided we extend the experiments over longer periods and make sure that the animals remain in equilibrium of nitrogen and carbon; *i. e.*, to be in a condition in which an amount of material will be actually oxidized in the organism that is equivalent to the food taken in. This question again depends, as we shall see, upon the law of the "conservation of energy" or as some preferred to call it, "the immutability of stored up energy." By energy we understand the ability to perform work. Daily experience teaches us that the particles of matter attain this ability when they are in motion. A leaden bullet held in the hand is a most innocent object, but when great velocity is imparted to it by the pressure from the gases of the explosion of powder in a gun, it will shatter bone and penetrate steel. Principles of mechanics teach that the energy thus produced can be measured by the work rendered and estimated as one-half of the product of the mass by the square of its velocity. What pertains to the leaden ball holds good for every other substance.

Imagine now two stones of equal weight, one lying on the ground, the other on the roof of a house, and that the latter by some cause is pushed over the edge of the roof. In falling it acquires an increasing rapidity according to Galileo's law. Upon striking the ground it can produce a certain effect or work which the other stone cannot. We see then, that besides *energy of motion*, there is another *energy of position*. The latter differs mainly from the former in that it becomes capable of giving off work when it passes over to energy of motion. It

has been therefore called *latent* or *potential energy* (older term was *elasticity*), whilst the first was termed *living* or *kinetic energy*.

Numerous experiments have demonstrated that energy of position (potential) is true not only for the mass forms of energy, but also for the smallest particles or molecules that go to make up the mass. This is known as chemical combination, but during this process there is a transformation from potential to kinetic energy—comparable to the transformation from the energy of position (potential) of a stone resting on a high place, and the same stone started on a fall downward toward the earth (energy of motion or kinetic energy). By the union of H and O molecules heat is formed, which is assumed to be due to change in the relative positions of H and O atoms. The amount of heat thus generated can be measured by appropriate instruments, just as the heat produced by the impact of a falling object has been measured. The molecules acting in a body seemingly at rest are assumed to be in continual movement, and the energy produced by this inward motion when exerted upon our nerves we designate heat. Now this form of energy may be transformed to the visible motion of masses or reversed, and here again the rule holds that the supply of energy is neither increased nor diminished. Finally, the same rule applies to all known forms of energy, electricity, light, chemical action, etc.

Single portions of this important law of nature were long known to physicists, but the general interpretation was first recognized, though perhaps defined in a vague manner, by the physician, Julius Robert Mayer, of Heilbronn. Helmholtz independently recognized the same law and gave to it a definite mathematic expression, summing up all actual proofs gathered up to that time. These have since then multiplied greatly, but not a single experience is found to contradict this law. We have to conclude then, that there is a supreme law of conservation of energy which substantially supplements the older law of the *immutability of matter*.

To explain the importance of this law for the better understanding of vital phenomena, I must add a word regarding the connection between heat and chemical processes. When in a mixture of H and O the molecules of these gases are set in motion with more or less rapidity, according to the temperature, the median distance between the molecules of these gases remains unchanged. If we apply a flame or electric spark to the mass, a mutual interchange takes place, H and O disappear and we have H<sub>2</sub>O instead, in which the H and O unite to form a new combination composed of the same molecules. This is known as a chemical union and may be likened to the process of the falling stone. Like this, the reciprocal position of stone and earth, in the latter the particles of H and O are changed, only that through this change heat is generated, a process that can be measured and estimated by means of the calorimeter. The potential energy (energy of the *position* of older writers) of the H and O particles is therefore converted into kinetic energy in the form of molecular motion which we call heat.

Many experiments have shown that in this union of the same quantities of H and O, one and the same amount of energy

is involved in the form of heat. One kg. of H oxidized into H<sub>2</sub>O produces an amount of heat that will raise 34,000 kg. of water from 0° to 1° C. This is known as the combustion heat of H and we may likewise so designate the combustion heat of C or that generated by any other chemical combination.

Strictly speaking, these figures are not the true expression of combustion heat between H and O. Important reasons lead us to assume that the atoms, the smallest particles in H, are not present in a free state, but united or coupled by twos to form one molecule, the same being true of the atoms and molecules of O. Before union can take place between the atoms of H and O to form molecules of water, the molecules of oxygen and hydrogen must be separated. Since this requires a certain amount of energy, the final result of this combustion is a slightly smaller amount of heat.

The combustion heat is equal to the combination heat minus the so-called molecular latent heat.

This condition must be more fully considered when it concerns complex instead of simple bodies. For instance, the fats are a combination of C, H and O. They are capable of taking on more O and are combustible into CO<sub>2</sub> and H<sub>2</sub>O. Lavoisier, as well as Dulong and Despretz, assumed that as much heat is generated as when equal quantities of free C and H are burned. As a matter of fact, however, the heat produced is smaller, due to the value of the latent heat in the atoms of C, H and O in the fat molecule. Just as heat is liberated by chemical union, we can analyze chemic compounds by heat. Red oxide of mercury is split into Hg and O on heating. The energy used up by this dissociation has always been found to be equal to the heat produced by combining the same elements in the same amounts. The law of conservation or immutability of energy applies here throughout.

After these lengthy digressions let us revert to the subject of living objects. Combustion goes on constantly in all animals. Substances containing C and H enter into them and free O is taken in with respiration, whilst both are given off in the form of CO<sub>2</sub> and H<sub>2</sub>O. Heat is thereby generated in all animals, even in the so-called cold-blooded, which are usually not warmer than their environment, because they give up their body heat more readily. Plants also form heat from the O, combining with C and H. In many blossoms—for example, the *Aroides*—in germinating seed and in other similar substances, the formation of heat may be so great as to exceed that which is lost.

Animals not only produce heat, but also produce mechanical work. In a large measure, this is accomplished by the muscles. This act takes place through the energy of chemical combinations. It has been shown that the process of oxidation is actively increased in the working muscles. Working persons excrete more CO<sub>2</sub> than those who are inactive. The animal machine which we call muscle is in this respect exactly like a steam engine, a part of the free energy given off appearing in the form of free heat, only that the muscle works under more favorable conditions than the best steam engine. Whereas in the latter only about 10 per cent of chemical energy can be utilized for work, this proportion may under circumstances



reach 25 per cent in the muscle. Count Rumford claimed that a pound of hay given to a horse will yield far greater utilization effect than when the same is used for fuel in a steam engine.\* (I have personal doubts as to the feasibility of such a comparative caloric test with the imperfect apparatus available in Rumford's days.)

The mechanical energy generated by combustion in the animal, when not used outwardly for work, is again converted into heat and therefore does not come into consideration in calorimetric investigations, where the animal is confined in a calorimeter. If, however, the experiment is conducted in such a way that some amount of the result is taken up in work, a correspondingly smaller portion of heat is set free, according to the above theory. Hirn, the physicist, has attempted experimentally to prove and estimate this mechanical heat equivalent from the relation between heat and work, but his experiments are not sufficiently exact to claim validity in comparison with the value of the heat equivalents obtained by other methods. In the United States Atwater and Benedict have solved this problem more successfully. For the modern physiology of this subject, see Howell, p. 963, sixth edition.

Animals obtain carbohydrates for nutriment from plants and give off the same in combination with O as CO<sub>2</sub>. Plants take up this CO<sub>2</sub>, split up the same and excrete it as O. Whilst energy is set free during the formation of CO<sub>2</sub>, this must be utilized in the dissociation of the same. This energy is manifestly derived from the sun, since the splitting up of CO<sub>2</sub> can take place only in light. There is no doubt that the great heat of the sun represents an enormous storage of energy. A portion of this reaches the earth by radiation and so far as it concerns the green plants it is stored up in the manner described. This not only serves to sustain animal life, but must also serve to liberate heat energy when parts of plants or organic material are burned in stoves. With regard to coal and similar derivatives of plant life used for heating, it is well known that they are the result or effect of the sun's energy, which in part has reached this earth many thousand years ago. (See the "Origin and Evolution of Life" by Henry F. Osborn.)

All life then, animal and vegetable, comes from the sun. But whilst we may be justified in assuming a cycle of events, complete in itself for the organic world, we cannot explain the transformations of energy in the same manner. The energy given off in the form of heat by animals radiates into space in the same manner as the energy from the sun, which has served the purpose of heating the earth's surface. But animal heat thus radiated into space is returned to the sun in but infinitesimal proportions. If, therefore, there are no other special sources besides those of the sun by which we could replenish our supply of energy, and about which we know nothing, the day may presumably come when no more energy will

reach the earth. Then all life will cease and the hour hand of eternity will have performed one revolution.

We have arrived at the goal of our travels. Whilst the path was rough and difficult, we have reached a height from which an extensive view over a vast and rich field is presented to us. This path has been largely planned and laid out by Lavoisier, so that but one, it is true the boldest, achievement was needed to reach the climax, and that was by keen research to confirm the law of the conservation of energy.

From this height it is impossible to consider details more accurately. If we step down and carefully examine the field of biological research, we shall recognize the fruits of the labors of so many workers. No opportunity is afforded to mention all. We should find everywhere many actively engaged in gathering in new fruits, sowing seed for future harvests or collecting crops preparatory for future cultivation. We should understand how the aid of chemistry, physics, and the astonishing advances in microscopical technics have cleared up the views of life processes. Above all things our attention would be drawn to a fact of which Lavoisier and his contemporaries had no inkling: the conception of the generation of living beings from elementary organisms or cells. This knowledge first begun by Schwann in 1839 has made tremendous progress. Histology and experimental physiology have continued the examinations of cell structure, as the laboratories of the finer processes of life.

However, let us rejoice in our present possession of truth which will serve as a starting point for new discoveries. Lavoisier's work has helped greatly to put us in possession of these basal truths. Chemists have long ago agreed that Lavoisier is the founder of modern chemistry. You will also admit from the foregoing that physiology also looks upon him as a pathfinder and owes him thanks for some of the most treasured acquisitions. But he also had predecessors who pointed out the way to proceed. As early as 1681, John Mayow recognized that only a portion of the atmospheric air was capable of sustaining respiration and combustion, and that this portion must be contained in saltpetre, for which reason he called it "spiritus," "fixed air." (See also article on Albrecht von Haller, section on respiration, by John C. Hemminger in *JOHNS HOPKINS HOSPITAL BULLETIN*, March, 1908.)

Going back still further, Leonardo da Vinci, a man of comprehensive and marvellous mind, who combined the genius of an artist with the talent of the scientist, recognized that fire consumed air and that animals could not live in the air which could not support the flame. We must also note that before Lavoisier, Priestley in 1774 produced pure O, and showed that it was absorbed by the blood and that dark blood was rendered bright red by it and that this absorption may also take place through the membranes, an important factor in understanding respiration. Lavoisier has been criticized by Lord Brougham for not being fair in acknowledging the claims of his predecessors. This may be possible, but one thing is certain, it was he who first established the doctrine of respiration and of formation of heat in animals and presented it in such form that all of his successors were enabled to add many single

\* Count Rumford's real name was Benjamin Thompson. He was an American, born in Woburn, Mass., in 1753, and later on married Madame Lavoisier, the widow of the great French chemist of whom this article deals. (See *Leading American Men of Science*, edited by David Starr Jordan.)

details, it is true, but were not able to change the main fundamental principles.

*Addendum.*—As this article is intended more as a contribution to the history of biochemistry than a complete biography, I cannot go into the details of Lavoisier's unjust trial and execution, by the tribunal of the French Revolution in 1794. Lavoisier was guillotined with 21 others connected with the work of the "*Fermier Général*." After the execution the great Lagrange said to Delambre, "*Il ne leur a fallu qu'un moment pour faire tomber cette tête-et cent années ne suffiront pas pour en reproduire un semblable*" (Eloge de Lagrange par Delambre Mémoires de l'Institut 1812 PXIV).

#### BRIEF ABSTRACTS OF IMPORTANT PUBLICATIONS OF LAVOISIER

Experiments on respiration in animals and the changes which take place in the air passing through the lungs. (1777.) Œuvres II, 174-183.

Of all the phenomena of animal life none are more striking and none arouse the attention of the physicist and physiologist more than those which accompany respiration. Heated mercury absorbs about  $\frac{1}{6}$  its volume from the atmospheric air by calcination, the remaining air cannot sustain respiration and combustion. On heating the mercurial precipitate we obtain a gas, which when mixed with the rest of atmospheric air again resembles the latter. A sparrow when confined in an air mass of 31 cubic inches dies in 55 minutes; the volume of air is only slightly diminished, about  $\frac{1}{60}$ . The residue cannot serve respiration or combustion and renders lime-water cloudy. Caustic potash decreases the volume  $\frac{1}{6}$ , loses its alkaliescence, effervesces with acids and crystallizes; briefly, it has become united to "fixed air." What remains after this absorption behaves just like the air in which Hg became calcined; if the respirable portion of ordinary air be now added we again have the latter. Therefore only two things are possible, either respiration changes the "respirable air" into "fixed air" (which Lavoisier calls *acide crayeux*, because it may be developed by treating chalk with acids) or an interchange takes place. [He inclined to the latter view because "respirable air" changes the blood to a red color like the metals (Hg, Pb, Fe) in calcination, but believes that both occur.]

No. 4, p. 537. On the combination of "fire material" (*la matière du feu*) with vaporous fluids and the formation of aeriform elastic fluids. (1777.) Œuvres II, 212-224.

An evidence of Lavoisier's inclination to the phlogiston theory. The author is of the opinion that there exists a very fine substance which he calls "matter of fire, of heat and of light" (*matière du feu, de la chaleur et de la lumière*) which permeates all bodies, forming with them an equivalent weight, not readily penetrable by each, and that this fluid exists in part free and in others (material bodies) in combination. The supposition is not new and its admissibility is proved by the conformity of the phenomena of which he treats and the fact that it explains all experiences of physics and chemistry. As with water with which a chemical combination is conducted, for example, in adding an alkali to an acid solution to form a neutral salt, a double rôle is played, in that a portion of the same enters into the combination, the other portion taking up the salt contained in the solution, keeping the particles of the salt apart, so that each part of the fluid contains an equal portion of the salt, so with "fire material" which permeates each body, a portion of which is in combination and the other free, keeping apart the particles of the body. In bringing together different substances, and chemical dissociation or union takes place, it depends upon whether or not the new

formed substances require as much "fire material" as the original; in the latter case heat must either be set free, which is noticed in the result, or it is abstracted from the surrounding bodies. Since all bodies take up "fire matter," measurements of the same cannot be determined exactly. All vessels are also lined with pores through which "fire matter" passes in, so that it cannot be measured like a fluid or gas shut off. Cooling sets in upon evaporation, as shown by Richmann, Mairan, Cullen and Baumé, and vapors are therefore produced by the union of fluids with "fire matter." Descriptions of experiments which he made conjointly with Laplace on the evaporation of fluids under the cell of the air-pump and refutation of the claims of the heat given off from limestone and effervescing alkalies by addition of acids are also given.

Mémoires sur la combustion en général. (1777.) Œuvres II, 225-233. No. 7, p. 538. Memoirs on heat (Lavoisier and Laplace, 1780.) Œuvres II, 283-285.

This work is in four parts. In the first the terms "free heat," "heat capacity" and "specific heat" are defined.

The authors do not decide between the two hypotheses on the nature of heat; according to one it is an imponderable fluid, whilst the other asserts that it is due to oscillation of the matter. They claim, what may be true of both views, the unchangeableness of free heat by simple mixture of the bodies, whereas in chemical processes it may be increased as well as diminished. At any rate we may formulate the rule that every change of heat, whether real or apparent, occurring in any alteration of the bodily system, must appear in inverted order when that body assumes its original state. They designate "heat unity" as the amount of heat necessary to raise 1 pound of water to  $1^{\circ}$  on the scale of  $80^{\circ}$ ; they term "heat capacity" or "specific heat" the relative heat units required to raise equal masses of different substances to an equivalent number of degrees. Conditions may vary in different temperatures, but it may be inferred that it is sufficiently constant within the limits of  $0^{\circ}$  to  $80^{\circ}$ . Since the admixture method is not sufficient to determine the specific heat, they show how it may be measured by means of ice, and describe the theory of development of the ice calorimeter and the apparatus employed.

In the second part the value of specific heat is considered with reference to water for a number of substances; further, the heat which is generated by mixing  $\text{H}_2\text{SO}_4$  and  $\text{H}_2\text{O}$ , Ca with  $\text{H}_2\text{O}$ , Ca with  $\text{KNO}_3$ , the combustion of various substances and the heat developed in a guinea-pig.

The third part consists of hypothetical considerations foreign to our subject.

In the fourth part heat from combustion of coal and the amount of  $\text{CO}_2$  is again estimated and compared to that produced in a guinea-pig and the air expired. The comparison of value as to conformity is sufficient to warrant the conclusion that respiration is a form of slow combustion, and similar to the burning of coal. The heat generated by the lungs is taken up by the blood and distributed throughout the body, and, like Crawford, the authors believe that the difference of heat capacity between arterial and venous blood also contributes to this. From all this they hold that the maintenance of an equal temperature in animals, with constant loss going on, is in great part due to the generation of heat by the union of the inspired "pure air" with the bases of the "fixed air" furnished by the blood.

Nos. 11 and 12, pp. 539 and 540. First memoir on respiration in animals. (1790.) Œuvres II, 688-703. Premier mémoire sur la respiration des animaux. First memoir on respiration in animals. (1790.) Œuvres II, 704-714. Premier mémoire sur la respiration des animaux.

These two works of Lavoisier and Seguin give a more exact description of their former experiments on respiration and animal

heat. In the experiments of Laplace and Lavoisier the amount of heat produced in animals was found to be somewhat greater than the  $\text{CO}_2$  given off. The account for this L. (1785) gave his opinion that probably some H besides C was burned during respiration. Respiration goes on in pure O and in a mixture of O and N under various conditions precisely in the same manner as in atmospheric air. N is neither absorbed nor excreted, but can be replaced by other indifferent gases. The amount of O taken up is greater in a lower temperature and is increased during digestion and muscle activity. The bodily temperature changes but little in the latter, but the pulse is accelerated in almost direct proportion to the amount of work yielded, so that other exertions, not measurable, such as recitation, composition, etc., may be determined thereby in a mechanical way. The average amount of O used by a man in 24 hours is estimated as 2 lbs. 1 oz. 1 dr., the C excreted as 10 oz. 4 dr., and the H (calculated as indirect from the superabundant O) as 1 oz. 5 dr. 51 gr. The article closes with observations on the nourishment of the working classes, regulation of heat and disturbances of weight equivalents.

For the examination of cutaneous transpiration they used an air-tight covering for the entire body, respiration being conducted by means of a tube in mouth. They differentiate between pulmonary respiration and transpiration. They surmise that carbonaceous and hydrogenous fluid is transpired in the blood of the lungs and then burned. With the  $\text{CO}_2$  and  $\text{H}_2\text{O}$  thus formed the water is evaporated as excreted by the blood. The latter is lung transpiration water, the former lung respiration water. To estimate these separately, water is calculated from the O and C, with the proviso that all  $\text{CO}_2$  originates in the lungs or the blood whilst circulating in the vessels. The sum total of respiration and transpiration is formed by weighing before and after the experiment, and the part taken by the lungs alone by weighing by means of the apparatus before and immediately at the end of the experiment, the difference then shows the part played by the skin. The authors are not deceived by the uncertainty of this hypothesis.

A résumé of all the published work by Lavoisier was given by Seguin alone in 1814.

## ABSTRACTS OF PAPERS

Representing Work Done in The Johns Hopkins Hospital, but Published or to be Published Elsewhere than in the Bulletin  
Prepared by the Authors

### THE INFLUENCE OF ACID PHOSPHATE UPON THE ELIMINATION OF AMMONIA IN THE URINE

W. MCK. MARRIOTT AND JOHN HOWLAND

(From the Department of Pediatrics, The Johns Hopkins University)

In the course of nephritis, acidosis may develop, but the evidences of acidosis differ from those usually found, in that there is no increase in the ammonia of the urine. It would seem from this that the acid responsible for the disturbance of acid base equilibrium in nephritis is different in character from those causing acidosis in other conditions.

We have previously shown that in nephritis there is an accumulation of inorganic phosphate in the blood plasma, due presumably to a failure of the kidney to excrete acid phosphate. We wished to determine, therefore, the difference, if any, in ammonia production resulting from the ingestion of acid phosphate and hydrochloric acid in equimolecular amounts.

The subjects were four normal men. Each was on his usual diet throughout the experiment which continued over 12 days. There was a preliminary period of three days. During the fourth day each subject drank 500 c.c. of decinormal hydrochloric acid. Following this there was a "normal" day. On the third day each subject took the equivalent of 500 c.c. of decinormal acid sodium phosphate ( $\text{NaH}_2\text{PO}_4$ ). On the following day 1500 c.c. of decinormal acid sodium phosphate were taken by each subject. Two "normal" days followed and then each subject took a solution of sodium phosphate having a pH of  $10^{-7.4}$ , that is, the reaction of the body, and containing exactly the same amount of  $\text{PO}_4$  as the 500 c.c. of decinormal acid phosphate. On the following day 1500 c.c. of decinormal neutral phosphate were taken. A subsequent "normal" day completed the experiment.

In the table are shown the average values for some of the important factors. From the results, it appears that hydro-

	Vol. in c.c.	pH	A*	$\text{NH}_3^*$	A $\text{NH}_2$	TN gms.	P gms.
Normal .....	1570	6.15	262	381	0.68	13.5	0.98
Normal .....	2100	6.4	279	386	0.71	13.2	1.06
Normal .....	1250	5.9	328	380	0.86	13.7	1.08
500 c.c. $\frac{N}{10}$ HCl .....	1860	5.5	404	529	0.76	13.5	1.05
Normal .....	1410	5.8	310	437	0.71	12.7	.98
500 c.c. $\frac{N}{10}$ Acid Phos. ....	1890	6.05	476	422	1.13	14.7	1.98
1500 c.c. $\frac{N}{10}$ Acid Phos. ....	2400	5.8	956	439	2.17	13.3	3.91
Normal .....	1570	5.85	512	433	1.19	12.4	1.88
Normal .....	1130	6.1	273	358	0.76	11.8	1.11
500 c.c. $\frac{N}{10}$ Neut. Phos. ....	1660	6.5	367	319	1.14	11.5	2.03
1500 c.c. $\frac{N}{10}$ Neut. Phos. ....	1690	6.8	323	238	1.36	12.9	3.65
Normal .....	1860	6.7	295	319	0.93	12.4	1.81

\* A represents the total titratable acid for 24 hours and  $\text{NH}_3$  the total urinary ammonia, each expressed in c.c. of decinormal solution.

chloric acid administration increases distinctly the ammonia coefficient in the urine and at the same time the titratable acid increases in about the same proportion, so that the  $\frac{A}{\text{NH}_2}$  ratio remains essentially unchanged. On the other hand, the administration of acid phosphate equivalent in titratable value to the hydrochloric acid led to absolutely no increase in ammonia excretion, and even three times this amount (1500 c.c.) failed to increase the excretion of ammonia. There was, however, a great increase in the titratable acid of the urine that the  $\frac{A}{\text{NH}_2}$  ratio increased greatly, reaching a point corresponding to that observed by Henderson and Palmer in severe nephritic acidosis. It would appear that the presence of phosphate in the body actually inhibits the production of ammonia, since hydrochloric acid alone leads to a great increase and the administration of 500 c.c. of decinormal acid phosphate is essentially the same (except for inert sodium chloride) as the administration



of an equivalent amount of neutral phosphate to which 500 c. c. of decinormal hydrochloric acid has been added. We should suppose, then, that the administration of phosphate at exactly the reaction of the body should decrease the ammonia excretion of the normal person and our results show this to be the case. There was a decrease in the excretion of ammonia after taking neutral phosphate and the  $\frac{A}{NH_3}$  ratio became greater than that seen in the normal person.

The experiments reported show that the presence of acid phosphate in the body, even in the absence of renal disease, gives rise to the excretion of urine of a character such as has been previously observed only in nephritic acidosis. It is our opinion that these results give additional confirmation to the view that the acidosis occurring in the course of nephritis is due to the retention of acid phosphate.

#### THE EFFECT OF ALKALI AND MALT PREPARATIONS UPON THE RETENTION OF CALCIUM IN INFANCY

By AKIRA SATO, M. D.

(From the Harriet Lane Home and from the Department of Pediatrics, The Johns Hopkins University)

This investigation was undertaken to see if an alkali has any beneficial influence upon the retention of calcium in an infant (as Dubois and Stolte (1913) reported in their article) and if carbohydrate has an unfavorable effect upon calcium storage, as some authors believe. Eight experiments were made upon the same infant with the same amount of milk as the diet. In some periods, sodium bicarbonate was added and in others, preparations of malt both with and without the alkali. The results were as follows:

The addition of an alkali produced not only no favorable effect upon the retention of calcium, but a distinctly unfavorable one, whereas malt extract alone without alkali acted beneficially upon calcium storage. Malt extract with a considerable amount of alkali produced a rather unfavorable result. It was therefore concluded that, if malt soup has a favorable effect upon calcium metabolism, it is not as a result of the alkali originally contained in it or added to it.

#### A RAPID MICRO-METHOD FOR THE DETERMINATION OF PHOSPHATE AND TOTAL PHOSPHORUS IN URINE AND STOOLS

By AKIRA SATO, M. D.

(From the Department of Pediatrics of The Johns Hopkins University)

The method is a colorimetric one and depends upon the precipitation of phosphate by uranium. The precipitated phosphate is dissolved in acid and the color, developed by the addition of potassium ferrocyanide, is compared with that produced by the same reagent with a standard uranium phosphate solution. For the determination 0.5 mgm. of  $P_2O_5$  is sufficient. Thus with the urine of the adult one would use 0.5 to 0.75 l. c. c., with the bottle-fed infant about 0.5 c. c. and with the breast-fed infant 5 c. c. But in each case a very simple test described in the original article should be made in order to determine the optimum amount of urine for the determina-

tion. The total phosphorus in the stools is determined in a similar way after digesting with sulphuric and nitric acids. In the analysis of theoretical solutions, the amount of inorganic phosphate was determined with an average error not exceeding 2 per cent. In that of urine and feces the method has yielded results differing by not more than 2 per cent from those obtained by the ordinary gravimetric method.

#### AN UNUSUAL COMBINATION OF CARDIAC ARRHYTHMIA WITH ATRIAL ORIGIN OCCURRING IN A PATIENT WITH FOCAL INFECTION AND THYROID ADENOMATA

By LEWELLYS F. BARKER, M. D., and HENRY B. RICHARDSON, M. D.  
(To be published in full in The Archives of Internal Medicine)

The paper describes a patient, aged 51, who for three or four years had presented nervous symptoms (insomnia, depression, weakness) and circulatory symptoms (dyspnoea on exertion, tachycardia, palpitation).

On physical examination he showed slight cyanosis, tachycardia, slight hypertension—blood pressure 145 systolic, 80 diastolic—eye signs of hyperthyroidism, oral sepsis, slight nodular struma, palpable liver, undescended left testicle. The blood was normal, the Wasserman reaction was negative, the stomach juice was normal, the urine showed a faint trace of albumin, but no casts. On X-ray examination there was slight clouding of the right atrium. Teleröntgenogram measurements: M. R. 6.7, M. L. 9.1. The adrenalin test showed rather marked hypersensitiveness to this substance. There was chronic tonsillitis and a moderate degree of benign prostatic hypertrophy without residual urine.

Electrocardiographic studies showed, at one time or another, the following: (1) Physiological rhythm; (2) dislocation of the pacemaker from the sino-atrial node to points elsewhere in the atrium; (3) alternate atrial extrasystoles, none of which provokes a ventricular response; (4) alternate atrial extrasystoles, many of which provoke a ventricular response; (5) paroxysmal tachycardia; (6) atrial flutter.

After removal of the oral sepsis, treatment of the paranasal sinusitis and a partial strumectomy, with general upbuilding measures, the patient markedly improved and the cardiac arrhythmia disappeared except for occasional extrasystoles. In the fuller report the bibliography is reviewed.

#### A NOTE ON THE SUPPOSED RELATION OF THE SYMPATHETIC NERVES TO DECEREBRATE RIGIDITY, MUSCLE TONE AND TENDON REFLEXES

By STANLEY COBB

(From the Department of Physiology, The Johns Hopkins Medical School and the Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore)

(To be published in the American Journal of Physiology, July, 1918)

The question of the sympathetic innervation of striated muscle is still far from settled. As the evidence accumulates, the probability diminishes that a simple explanation of tonus has at last been found. For a time the researches in anatomy and physiology had made it seem probable that tonic muscular contraction was due to sympathetic innervation. In this work

some experiments of deBoer and Dusser de Barenne were modified and repeated. A series of experiments was done on frogs to test deBoer's observation that cutting the rami communicantes of the abdominal sympathetic in frogs causes a loss of tone in the ipsilateral leg muscles. Sixty-one frogs were operated on in different ways and although the simple cutting of the rami usually seemed to cause the leg to hang lower, no consistently corroborative evidence was obtained from stimulation or degeneration experiments. Seven cats were operated on. In one case simple unilateral excision of part of the abdominal sympathetic chain was performed; the abdominal sympathetic was cut before decerebration in five cases, and afterwards in one case. The effect of stimulating the sympathetic chain was tried out, also the effect of inhibiting decere-

brate rigidity by cerebellar stimulation, with and without an intact sympathetic chain. Besides this, repeated observations were made on six cats, after their recovery from the sympathetic excision, to see if the muscular tonicity or tendon reflexes had been affected.

The following conclusions were reached:

- (1) Section of the abdominal sympathetic chain in cats:
  - (a) Has no effect on decerebrate rigidity, either by preventing its development or its inhibition.
  - (b) Causes no obvious hypotonicity of the hind legs or tail.
  - (c) Causes no change in the tendon reflexes.
- (2) Stimulation of the abdominal sympathetic chain causes no tonic contraction of the ipsilateral hind leg.

## NOTES ON NEW BOOKS.

*History of Medicine, Suggestions for Study and Bibliographic Data.* By FIELDING H. GARRISON, A. B., M. D., Principal Assistant Librarian, Surgeon General's Office, Washington, D. C. Second edition revised and enlarged. Octavo of 905 pages with many portraits. (Philadelphia and London: W. B. Saunders Company, 1917.)

The appearance of the second edition of Garrison's work is an index of the increased interest which has been aroused in the United States in the study of medical history. The first edition was a distinct advance on previous histories of medicine in the English language, and served a most useful purpose here and elsewhere. The additions and changes in the second edition bear remarkable testimony to the zeal, scholarship and industry of the accomplished author. The work has been revised, enlarged and made even more useful to the student of history than before. It deserves the widest circulation and the most careful consideration on the part of all persons who take any interest in the checkered past of medicine, or who are stimulated by the review to cherish hopes for the future. The book is admirably printed, and the proof reading has been excellent.

H.

*Syphilis.* By LLOYD THOMPSON, M. D. (Philadelphia: Lea and Febiger, 1916.)

The subject of syphilis is perhaps the most important one of all the great divisions in medicine to-day. As the author of the book aptly states this in the opening sentences of the preface, one must involuntarily agree with him; because, after all, some of the most brilliant researches and solutions of medical problems have been made by workers in this field in the past 15 years. Many of these conclusions, coupled with a more intensive study of the subject, have made us all so much more keenly alive and sensitive to this great problem that a book of this character can of a certainty lay a claim to some kind of recognition.

Books dealing with syphilis have always been available, varying from the chapter in the average text-book, devoted to syphilitic manifestations of the special field under consideration, up to the large systems which are, of course, encyclopedic in character. However, there is always a place for an up-to-date book which is concise, brief and yet sufficiently comprehensive to make it a thing for ready and satisfying reference.

This book should appeal particularly to the student because it deals quite broadly with the entire subject; and as stated, is certainly handy for reference for the busy teacher. It is very commendable that the author has given a decidedly interesting though necessarily brief history of the disease, and of the advance-

ment of our present-day knowledge of it; and that he has added an interesting chapter on the importance of syphilis is a genuine advantage.

In one sense the book is encyclopedic in character, even though the discussions are not entirely comprehensive; but its very brevity in this respect is perhaps a real asset. The last part (III) devotes nearly 40 pages to a description and treatment of congenital syphilis—much of which is of necessity a repetition of what has gone before.

Among some of the noticeable features to which attention might be directed are the persistent references to the great importance of the Wassermann blood test—a factor which is, of course, of inestimable value, but which, if emphasized too much, might tend to discredit and to discourage a keener study of the clinical aspects of the disease—the very thing which permitted such men as John Hunter, Ricord, Fournier, Erb, Jonathan Hutchinson, etc., to become the great masters. We must never relax our clinical vigilance with a subject such as this, and should rely on laboratory tests rather as adjuvants.

There are a few minor defects in the text, such as typographical errors, in the misspelling of proper names and of drugs (aspirin for aspirin), as well as in the use of terms (tubercular for tuberculous). However, the book has the decided advantage of bringing together in one volume all phases and aspects of the subject in proper co-ordination and good arrangement. Furthermore, it supplies what we consider an important essential for a text-book, namely, brief but significant additions culled from the author's personal experience.

Without taking up the various chapters, we would mention merely the excellent and clear expositions of laboratory technique; the helpful and not too numerous references as foot-notes; and the splendid, comprehensive, yet concise descriptions on pathology, especially of the skin manifestations.

The book is attractively presented, in very handy form; the photographs of the skin lesions are adequate but not unusual, and on the whole the book should become a necessary part of every medical student's library.

With the rapid advancement in our knowledge of syphilis of the nervous system, the appearance of the book is very timely. Much has been accomplished, especially in the matter of treatment, since the publication of this volume. The treatment of these manifestations is at present passing through a stage of trial, and judging from results published by various authors much is to be hoped for.

We, therefore, look forward to the appearance of a subsequent edition of this book with much anticipation and assurance.

I. R. P.

# BULLETIN

OF

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## STUDIES ON THE ASEPTIC END-TO-END ANASTOMOSIS OF THE INTESTINE

By ERNEST G. GREY, M. D.,

*Assistant Resident Surgeon, The Johns Hopkins Hospital*

*(From the Hunterian Laboratory of The Johns Hopkins University)*

For many years attempts have been made by surgeons to devise practical methods for the end-to-end anastomosis of the intestine which would minimize the amount of soiling of the suture line and of the neighboring abdominal structures. As a result, a number of interesting suggestions have been made by Pochhammer,<sup>1</sup> Werelius,<sup>2</sup> Flint,<sup>3</sup> Rostowzew,<sup>4</sup> Moszkowicz,<sup>5</sup> Gudin,<sup>6</sup> Wullstein,<sup>7</sup> and by others. The methods to which the best clinical results have been ascribed, however, have all made use of instruments, all or some of which had to be extricated from the line of closure in the concluding steps of the operations. Such procedures, of course, either leave the lumen temporarily occluded with crushed bowel, or expose the line of anastomosis to soiling from within.

A short time back Professor Halsted<sup>8</sup> suggested the bulkhead suture for this purpose—a procedure which was altogether novel at the time, and which afforded certain distinct advantages over the methods then in use. He demonstrated on dogs that a successful end-to-end anastomosis of the intestine might be carried out in an aseptic manner, "except as contamination may occur from stitches which of necessity or by accident have been carried into the lumen of the intestine." Until some substitute is discovered for the needle and thread it will be necessary always to reckon with this source of contamination. The fact, however, that with care the operator may prevent most or all of the stitches from entering the lumen greatly lessens the importance of this factor.

The experiences presented in this report were encountered in the course of some experiments with this method conducted on dogs. Although the procedure described here differs from that used by Professor Halsted in certain details, it nevertheless makes use of the characteristic feature of the bulkhead suture, namely, the invagination of the closed ends of the intestine with subsequent cauterization of them to re-establish the lumen. The wire-release ligature and the fibrin bolus have been substituted for the cones of paper.

The absence of any recorded microscopic examination of intestinal anastomoses made with the bulkhead suture suggested to the author the desirability of comparing the rate of healing in such anastomoses with that occurring in the simple, open, end-to-end unions of the bowel. Such a study, it was thought, would also afford some opportunity to observe the effects of the use of the cautery on the rate of healing in intestinal wounds.

### METHODS

*The Fibrin Bolus and the Wire-Release Ligature.*—The fibrin bolus is prepared from ordinary blood fibrin after a method developed by Dr. S. Harvey,<sup>9</sup> of Boston. In a former communication,<sup>10</sup> I suggested the use of fibrin for controlling the extensive hemorrhage which sometimes follows the removal of a cerebral tumor having deep or extensive attachments to a neighboring sinus. Harvey subsequently



is used a method by which microscopical dissection of the gut might be used for hemostasis.

The vascular fibrin obtained from wallpaper freshly drawn blood at the abattoir is ground up to a fine pulp. This pulp is then made into sheets of any desired thickness by drying a layer in a high-power press. A sheet of this material is cut into small rectangular pieces of such a size that two or three will just occlude the lumen of the canine gut. To engage the ligature a shallow notch is made in each a few millimeters from one end.

These blocks stand steam sterilization well, retaining their shape and firm consistency. In a flask stopped with cotton they may be preserved indefinitely. Since they are digestible—in the course of several days or a week—they do not act as real foreign bodies in the alimentary tract.

The wire-release ligature is a simple contrivance which may be prepared rapidly at the table from the ordinary supplies of the operating room. Two lengths (each of about 14 inches) of extra heavy silk are used. Each is doubled once at its middle, and the folded ends of the two are interlocked over the end of a fine piece of wire, such as is used as a stilette in a large hypodermic needle (see Fig. 5). When the ends are drawn taut the threads bind the wire, and they may be tied around the bowel and bolus with a considerable degree of tension.

To release the ligature the bowel is gently supported over the region of the knot. The wire is then twisted a little back and forth in its longitudinal axis while traction is made upon it away from the gut. The thread ends now fall apart. The wire may be removed in this fashion without causing any trauma to the intestinal wall. As the bulkhead occupies the bowel immediately subjacent to the ligature there is no question of leaving the lumen occluded.

*The Operative Technique.*—The first step in the operation is identical with that described by Professor Halsted (Fig. 1). At the point of election the peritoneal and muscular coats are divided and stripped back on the submucosa far enough to enable the operator to place two ligatures around the gut. The intervening submucosa and mucosa are then divided with the cautery.

To prepare the bulkhead two or three of the fibrin blocks (depending upon the size of the lumen and the dimensions of the blocks) are held together and pressed against the cauterized end of the bowel invaginating it to the desired extent (Fig. 2). It saves time in the subsequent steps of the operation when the blocks are invaginated so that their exposed ends lie a few millimeters within the folded margins of the bowel. The wire-release ligature is now tied with force a short distance from the end of the intestine, binding the gut to the enclosed bolus. It is so placed that the free end of the wire is directed away from the line of anastomosis. After both pieces of intestine have been prepared in this way, the folded ends are cut away with the cautery-knife close to the ligatures, as in the Halsted method (Fig. 3).

As the vessels have not been disturbed in these steps the blood supply remains perfect up to the site of each ligature.

Exactly at this line the vessels entering the gut are ligated. The larger vessels distal to this point are then also secured with circumvection ligatures. The end-to-end anastomosis now remains to be made with the continuous mattress suture (Fig. 4). An additional mattress stitch placed about each release wire is drawn tight only when the latter is removed. The wires in the course of the anastomosis find their points of exit without interfering with the approximation of the bowel ends.

The ligature about each bulkhead having been released by the withdrawal of the wire, the line of union is gently rolled in a piece of gauze to loosen the boli. With slight pressure the invagination bulkheads are liberated and the lumen of the bowel is re-established.

#### OBSERVATIONS

*The Operative Results.*—The operation as described here was performed on 37 dogs—34 times on the small intestine and three times on the colon. The specimens were removed at varying postoperative periods ranging from 48 hours to 106 days. In the series of 37 animals there were two deaths directly attributable to the work on the intestines. Post-mortem examination in both instances disclosed a general peritonitis, the origin of which could be traced to a perforation in the line of anastomosis. Each of these animals, however, was quite small, with a bowel proportionately narrow in its diameter.

Two great principles are now recognized in intestinal surgery. The first, inculcated by Lembert,<sup>1</sup> is to rely on the serous coat to procure early and permanent adhesions; and the second, pointed out by Dr. Halsted, is to include some of the submucosa in the sutures, since the submucosa is the strongest coat of the bowel wall. Where the intestine is very small, as in the two animals just referred to, it is difficult to secure the proper approximation of the serous coats, because the inversion of any appreciable amount of bowel usually results in an occlusion of the intestinal lumen. A weak serous apposition, of course, predisposes the part to subsequent leakage. This is particularly the case where there is some encroachment upon the intestinal canal, since the latter condition always leads to more or less stasis in the proximal segment.

In larger animals very little difficulty of this nature is encountered. Human bowel should be still more favorable for this type of anastomosis, because the width of the intestine is greater and there is more of a difference in the ratio of the diameter of the gut to the diameter of its lumen.

To make the method applicable to the human colon it would be necessary to devise certain modifications of the fibrin bolus. The diameter of the bolus would have to be greatly increased, since the diameter of the canal at the line of anastomosis in the bulkhead suture is determined, in a large measure, by the dimensions of the supporting framework—the paper cone or the blocks of fibrin.

In the course of some work with the large intestine of the pig, procured from the abattoir, it was found that a bolus of

ample proportions might be constructed from fibrin by fastening together a considerable number of small blocks with a wire-release ligature. After such a support has been secured in the bulkhead by means of the usual release ligature placed around the gut, the wire of the bolus may be withdrawn, leaving the fibrin blocks secured only by the external tie. The release of the invaginated bowel ends, subsequent to the anastomosis, ultimately permits the pieces of fibrin to separate. In this form they should be well cared for by the intestine.

The modified Halsted suture suggested in this report represents, then, a practical technique for the aseptic end-to-end anastomosis of the small intestine, since all of the materials may be sterilized readily and since the experimental work has shown that a dog's life is not greatly endangered by the operation. The technique is suggested, however, solely as a step toward the solution of the problems connected with the anastomosis of the large intestine. It is in operating upon the colon, of course, that the greatest danger of peritoneal infection arises. Experiments on the living animal having to do with a colon of the human type could be carried out only in the larger animals, such as the pig or the sheep.

*The Healing of the Bulkhead Anastomoses.*—During the course of the first few hours subsequent to the operation the serous surfaces become glued together with a fibrinous exudate. This exudate, as Halsted<sup>23</sup> and Mall<sup>24</sup> first pointed out, appears even before the anastomosis is completed, and serves to seal the stitch holes. Evidences of a reaction on the part of the tissues to the trauma sustained during the operation now make their appearance in the form of edema, infarct formation, leucocytic infiltration, etc.

All of the specimens of 48 hours show comparatively large flaps of inverted bowel wall—an inherent feature of the bulkhead method. These inturns, however, are not all of the same size, but vary somewhat from animal to animal. The largest of all was present in an anastomosis which had been made, for comparative purposes, with a knife instead of a cautery. The other steps of the bulkhead operation had been carried out as usual.

At the end of two days the condition of the inturn depends upon the condition of its vessels and upon the amount of injury to which it was subjected. When through either or both of these factors the viability of the inverted tissues has been seriously affected, a slough starts to form which varies in extent throughout the circumference of the bowel. The rapidity with which the slough separates and the mucosa covers the ulcer depends, of course, upon the extent of the necrosis. It is this factor, namely, this extent of the slough, which chiefly influences the rate of healing. Of much less significance in this respect is the size of the inturn.

At 48 hours (Fig. 6) the inverted bowel wall is edematous and hemorrhagic, and at the base of the flaps there are changes suggesting necrosis, particularly of the epithelium. The muscularis mucosæ on either side can be traced out to the end of the inturn, but it soon appears edematous. A corresponding swelling is evident in the submucosa. Shortly beyond the base of the inturn the muscle coats become hemor-

rhagic, swollen and infiltrated with leucocytes. At the suture line, extending up between the serous surfaces of the bowel ends to the level of the muscularis mucosæ, is seen the fibrinous exudate. This serves to smooth over the external surface of the anastomosis.

Sections from certain other 48-hour specimens show a less extensive sloughing of the inverted parts. As a rule, the inturned ends are about equally affected. Occasionally, however, owing to poor approximation of the segments or to extensive unilateral necrosis, the two flaps may be of very unequal length. When the flaps are of unequal length there is, of course, a great delay in the process of healing, especially of the mucosa. In the instances in which the knife was substituted for the cautery there is again a variation in the picture from specimen to specimen. It is this variation which makes it difficult to estimate the effects of the cautery on the process of healing. On the whole, there seems to be very little difference between the two sets of specimens.

At seven days (Fig. 9) the stage of sloughing has passed and the process of repair is fairly under way. The inturn is now surmounted by an ulcer, the bed of which consists of partially organized exudate. Quantities of polymorphonuclear leucocytes and round cells are present together with many young connective-tissue cells and newly formed blood-vessels. At the borders of the ulcer the epithelium is low and undifferentiated in type. Villi are found only at some distance from the uncovered area. The stratum fibrosum is visible on the left up to the edge of the mucous membrane. Here it lies exposed. On the right side the end of the stratum fibrosum is covered by the flattened epithelium. The muscularis mucosæ has a fairly normal appearance up to the region where the epithelium becomes embryonic in type. Its identity is then lost in the scar tissue. The submucosa on one side is considerably thickened; both of the layers, moreover, are denser than usual, owing to the presence of new connective-tissue cells and young blood-vessels. A very appreciable amount of new fibrous tissue is scattered throughout the muscle bundles of the inturn. The muscle layers are also infiltrated with white blood-cells in places, the reaction assuming its greatest proportions in the immediate vicinity of the stitches. This picture is very similar to Gould's<sup>25</sup> 5-day stage (plain end-to-end anastomosis of the intestine), to Halsted and Mall's<sup>26</sup> 6-day specimen (entero-enterostomy), and to Flint's<sup>27</sup> 7-day suture (gastro-enterostomy).

A section from another part of the same specimen shows a much more advanced stage of healing. Here the mucosa has practically covered in the ulcer. The epithelium over the exudate is of the low, undifferentiated type, containing a few shallow crypts, but no villi. The stratum fibrosum and muscularis mucosæ may be traced up to within a very short distance of the line of union of the epithelial layers. They now extend, accordingly, a little beyond the region where the villi disappear. Toward the base of the anastomosis the muscle layers are found to be separated by a moderately broad band of scar tissue, comprising crushed muscle bundles, new connective-tissue cells, and white blood-cells. This picture closely

resembles the 24-day specimen of Halsted and Mall and the 8-day specimen of Gould.

In a section from a 14-day-old suture (Fig. 10) the ulcer is found to be converted into a mass of fibrous tissue which still shows a considerable degree of reaction; and this is completely covered by a low, atypical epithelium. Flint found little evidence of reaction at this time (14 days) save in the immediate neighborhood of the stitches. The cleft at the point of union of the two epithelial coats is sheathed by a single layer of low columnar cells. The stratum fibrosum does not completely bridge the scar tissue. Traces of fibers suggesting the muscularis mucosæ are visible on one side up to the midline. On the side of the cleft, however, this layer is indistinct for a short distance. The exudate between the deeper muscle layers has become definitely organized.

Another section from this specimen shows a somewhat less advanced stage of healing. Here a very narrow ulcer caps the intum. Muscle fibers, apparently from the deeper layers, are found scattered in the gap between the ends of the muscularis mucosæ. This corresponds to a 14-day specimen described by Flint in which the muscularis mucosæ had partially regenerated from each side, the intervening defect being filled in by muscle from the circular and longitudinal layers.

In a section from a 14-day plain end-to-end suture the picture is fairly similar, except that in this instance there is less of a diaphragm. The ulcer is covered at the center by a single layer of epithelial cells. The muscularis mucosæ and the stratum fibrosum here disappear close to the edges of the ulcer—rather far from the midline. Gould's 14-day specimen shows an intum fully as large as that seen in the 14-day bulkhead suture (Fig. 10).

How greatly the repair of the intestinal coats may be delayed by an inequality of the sloughing process in the two halves of the intum is indicated by the condition of a specimen which was removed at 21 days. A long, well-nourished flap remains on the left side. On the opposite side, however, no appreciable trace remains of the inverted bowel wall. The intum is covered on one surface by a fairly normal appearing coat of mucous membrane, but over the end and on the opposite face no epithelium is visible. So far as the function of the anastomosis is concerned the exposure of this area of granulation tissue probably has no especial significance. The line of suture, though, cannot be considered healed until the epithelial layers have united; and in a case such as this a number of additional weeks would be required to accomplish it.

An anastomosis 24 days old (Fig. 11) shows a very advanced stage of repair. In one section the ulcer is covered with a moderately high epithelium. Near the point of union some shallow crypts are visible. No villi, however, make their appearance here. The muscularis mucosæ reaches almost across the defect. In the region where the villi disappear the submucosa broadens out and merges into the scar tissue of the old ulcer. A section from another part of the circumference reveals a slight gap between the epithelial layers of either side. The muscle coats below are separated by a rather wide

area of scar tissue which still presents a considerable degree of infiltration.

There is no more heaping up of the coats at the line of anastomosis in this specimen than was noted by Dr. Halsted and Dr. Mall in their intestinal suture of 24 days or by Dr. Flint in his gastro-enterostomy of 55 days. More of the bowel wall certainly is inverted in carrying out the bulkhead operation than in making a plain end-to-end anastomosis. The similarity in the specimens, then, must be due to the fact that subsequently to the former procedure most of the intum had been cast off. From this it appears that a large intum may not materially prolong the healing time provided that the two ends slough to about the same extent.

A section from a plain end-to-end anastomosis of 22 days' duration shows a picture little differing from this except for an absence of most of the infiltration which characterizes the bulkhead suture. The 22-day section just referred to is very similar in appearance to Mall's 24-day suture (Fig. 10).

At 41 days (Fig. 12) the epithelium completely bridges the line of union. Here short crypts are present together with comparatively large villi. Over a rather wide area no muscularis mucosæ is discernible, but where one would expect to find it connective tissue and muscle from the deeper layers appear to be aligning themselves to form a substitute. A rather wide expanse of scar tissue is present in this specimen between the ends of the muscle coats. As the bowel is comparatively flat now at the site of the anastomosis, this separation of the muscle coats suggests the fourth stage of healing—the straightening of the suture—as noted by Mall in Halsted's sutures of 25 to 36 days. The process of healing in the bulkhead suture, accordingly, may, under favorable circumstances, lag but little behind that occurring in the plain end-to-end anastomosis.

Sections from a 50-day specimen are quite similar in appearance. A somewhat more advanced state of repair is seen in a 52-day plain end-to-end suture. The epithelium is of normal height throughout and the circular muscle coats are well approximated. There is only a very narrow break between the ends of the muscularis mucosæ.

From this period on, the villi and crypts at the anastomosis gradually assume more normal proportions. As the submucosa decreases in width the muscularis mucosæ become regenerated across the defect. The ends of the muscle coats at the same time approach each other and become bound together by a very narrow scar. The subserous scar slowly disappears (Figs. 13 to 15).

The rate of healing described above, however, is not characteristic of all bulkhead sutures, as has been emphasized before. Owing probably to the necessity of an extensive repair, the regeneration in certain places is considerably retarded. In a 57-day specimen one section shows an extremely narrow ulcer still existing at the line of union. Another section has a single layer of epithelial cells covering this site. The other coats are all well healed. A rather prominent intum remains still in a 77-day suture. The presence of the intum, however, has not interfered with the regeneration of the coats.



The rate of repair does not appear to be greatly influenced by the use of the cautery. In some of the earlier stages no appreciable difference was noted in this respect between the bulkhead sutures divided with the knife and those treated with the hot iron. Similar observations have been made by Scudder and Harvey<sup>16</sup> in their study of the use of the cautery in the treatment of gastric ulcers. At 105 days a suture in which the cautery-iron was used shows a slightly better regeneration of the mucous coat than a suture of 106 days in which the knife was substituted for it.

#### SUMMARY AND CONCLUSIONS

This report is based upon the results obtained from using the bulkhead suture (Halsted) in 37 dogs. A new wire-release ligature and a bolus of fibrin which is easily sterilized have been substituted for the paper cones. Specimens were secured following the operations at intervals varying from a few hours to 106 days. A study of the process of healing shows the following points:

The process of repair in the bulkhead suture may, under favorable circumstances, lag but little behind that noted in the plain end-to-end anastomosis. On the average, however, the healing is a little slower in the former.

A large intum may not materially lengthen the period of regeneration, provided that the two inverted bowel ends remain about equal in size. The size of the intum remaining after several weeks varies greatly from specimen to specimen. Frequently very little inverted bowel is found at this time.

As a rule, there is a considerable delay in the repair of the mucosa when the two parts of the intum are of unequal length—owing to poor approximation or to an inequality in the necrosis on the two sides. This, however, does not appear to affect the function of the intestine.

No striking difference was noted in the rate of repair between bulkhead sutures in which the cautery had been used and those in which the knife had been substituted for it.

Stitches which puncture the epithelium usually delay the healing of the latter. Frequently such sutures carry a prolongation of the epithelium down into the deeper layers. Such adenoma-like prolongations may weaken the line of union where only one layer of stitches has been inserted.

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## ANOMALIES OF THE PULMONARY VEINS

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Although anomalies of the pulmonary vascular system are by no means uncommon, the following three cases, met with during the course of dissection in the anatomical laboratory of the Johns Hopkins Medical School (1917-18), are so exceptional as to merit special mention, particularly in view of their possible embryological explanation. In two of the dissections the upper pulmonary vein of the left side opened into the left innominate vein; in the third case the upper pulmonary vein of the right side emptied into the superior vena cava.

In the first case, which is shown in Fig. 2, the left superior pulmonary vein passes through the hilum of the lung above the pulmonary artery. It pursues a course ventrad and cephalad and opens into the left innominate vein 1.5 cm. from the junc-

ture of the latter with the subclavian vein. It measures 3.5 cm. in length and is slightly smaller in diameter than the left inferior vein. It drained all of the upper lobe with the exception of a small area on the inferior medial surface, adjacent to the inferior lobe. This area was separated from the upper lobe by a fissure, and was at first thought to be a separate lobe. It had its own bronchus, its separate arterial branch and its own vein from the inferior pulmonary vein. However, the fissure proved to be entirely superficial and the separated area to be part of the upper lobe.

The vessels in the hilum of the lung occupy abnormal positions. The upper pulmonary vein lies above the pulmonary artery; below this is the bronchus, and below this, again, is the

inferior pulmonary vein. The last enters the left auricle in the normal way. As the veins from the right lung are normal, only three veins enter the left auricle.

The heart presents several peculiarities, the most noticeable being the relatively great size of the pulmonary artery. In view of the greater amount of blood it received, one would expect to find the entire right side of the heart enlarged, and the left side smaller in order to establish an equilibrium. This appeared to be the case, though it cannot be stated definitely, because in a preserved heart such as this exact measurements cannot be made.

The interventricular septum lies farther to the left than is apparent in Fig. 2. A notch in the lower border of the anterior wall of the right ventricle gives this false impression. The notch seemed to have no significance at all in the interior of the heart. One thing of importance, bearing directly as it does upon the discussion to follow, is the total lack of any left oblique vein of the heart.

The second case dissected is analogous to the one above described. In this the left upper pulmonary vein opens into the left innominate, and is thought to have drained the whole of the upper lobe, though its exact distribution was not ascertained at dissection.

In the third case which is shown in Fig. 3, the right upper pulmonary vein opens into the superior vena cava, near the opening of the azygos, and 1.5 cm. from the junction of the innominate veins. As in the second case, its exact distribution was not observable at dissection, though it was thought to have drained the entire upper lobe. The only other peculiarity noted was in the heart; here the orifice of the coronary sinus was located on the same side of the Eustachian valve as the inferior vena cava.

Report of various other cases of anomalous pulmonary veins have been published. Those in which there has been a communication between the pulmonary and systemic systems may be classified as follows:

#### FOUR WITH THE LEFT INNOMINATE VEIN

Two cases. Upper pulmonary vein of the left side opening into the innominate.

Thane, C. D., *Jour. Anat. & Physiol.*, 1906, xi.

Bachhammer (by Debierre), *Traité d'anatomie humaine*, 1890, t. 2.

One case. Additional pulmonary vein draining half of the upper lobe of the left side, opening into the innominate.

Looten, J., & Ruyssen, G., *Biblio. anat.*, 1910, xx.

One case. Vein draining upper two-thirds of the left lung into the innominate, with a branch to the accessory hemiazygos.

Patterson, J., *Jour. Am. Med. Assn.*, 1913, lxi.

#### SIX WITH THE SUPERIOR VENA CAVA

Five cases. Upper pulmonary vein of the right side into the superior vena cava.

Grueber (2 cases), *Arch. path. Anat.*, 1876.

Meckel, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

Gegenbauer, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

Winslow, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

One case. Left pulmonary vein into the superior vena cava.

Weber, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

#### THREE WITH THE INFERIOR VENA CAVA

Two cases. Upper right pulmonary vein into the inferior vena cava.

Brown, A. G., *Anat. Record*, 1913, vii.

Chassinat, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

One case. Five or six small upper left pulmonary veins into a small rudimentary vena cava.

Hyrtil, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

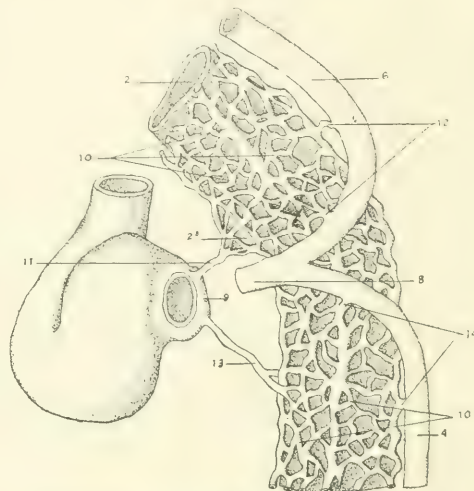


FIG. 1.—Reconstruction of a 4.5 mm. cat embryo. The left cornu of the sinus venosus has been removed.

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|----------------------------|--|
| 2. Intestinal tract.       | 11. Cephalic communication of the splanchnic plexus with the cephalomesial portion of the sinus venosus (common pulmonary vein). |
| 2a. Pulmonary anlage.      | 12. Communication between the splanchnic plexus and precardial vein.   |
| 4. Left postcardinal vein. | 13. Caudal communication of the splanchnic plexus.   |
| 6. Left precardial vein.   | 14. Communication between the splanchnic plexus and the postcardinal vein.   |
| 8. Left duct of Cuvier.    |  |
| 9. Sinus venosus.          |  |
| 10. Splanchnic plexus.     |  |

#### ONE WITH THE AZYGOS VEIN

One case. Single right pulmonary vein into a large azygos vein.

Sheperd, F. J., *Jour. Anat.*, XXIV.

#### TWO WITH THE SUBCLAVIAN VEIN

Two cases. Left pulmonary vein into the subclavian vein.

Weber, *Arch. Anat. u. Physiol.*, Leipzig, 1829.

Ramsbotham, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

Communications between the pulmonary and portal systems are exceedingly rare, only two cases being found in the literature.

#### TWO WITH THE PORTAL VEIN

One case. Right pulmonary vein into the portal vein while the left pulmonary vein opened into the subclavian vein.

Ramsbotham, *In Poirier & Charpy's Traité d'anatomie humaine*, 1901, t. 2.

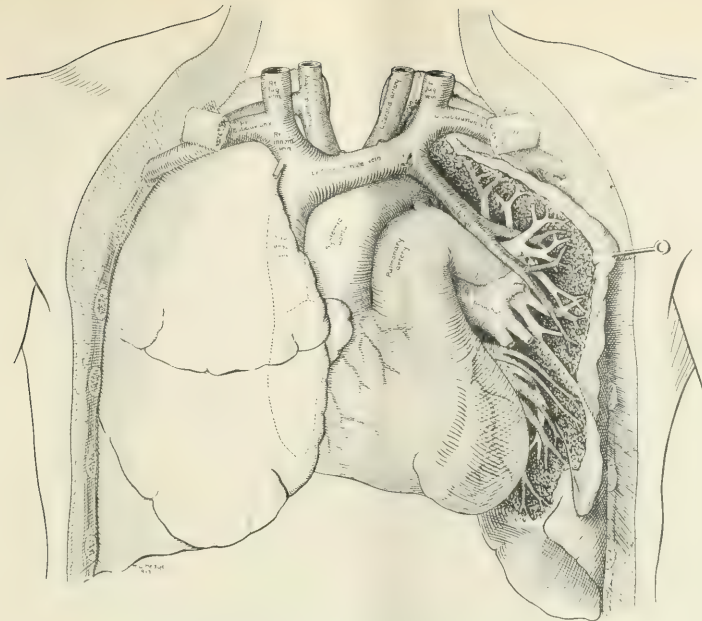


FIG. 2.—Case I in which the upper left pulmonary vein empties into the left innominate vein, 1.5 cm. from the junction of the latter with the subclavian vein. This abnormal pulmonary vein drained all the upper lobe of the lung with the exception of a small area adjacent to the lower lobe. This area was drained by a branch of the inferior vein and, as can be seen in the figure, was separated from the rest of the upper lobe by a shallow fissure. It was supplied by a separate branch of the pulmonary artery and a separate bronchus. There were but three pulmonary veins opening into the left auricle. The pulmonary artery is seen to be exceptionally large. A notch in the lower border of the anterior wall of the right ventricle gives a false impression as to the position of the interventricular septum. This lies further to the right than appears in the figure. The left oblique vein was entirely lacking. Case two was analogous to this one.

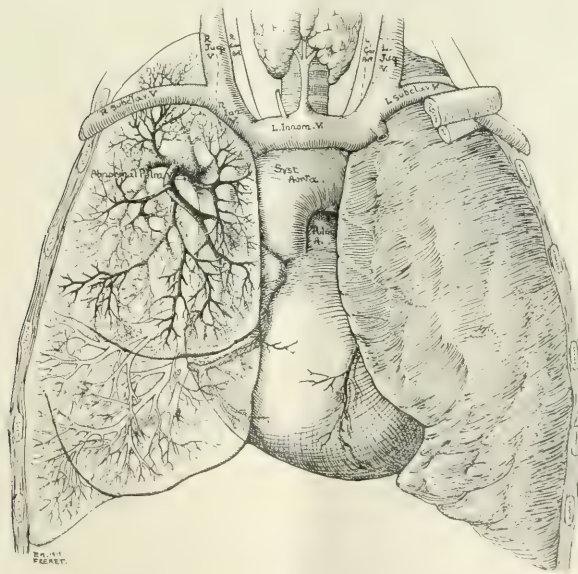


FIG. 3.—Case III in which the upper right pulmonary vein empties into the superior vena cava, 1.5 cm. from the junction of the innominate veins. It was thought to have drained all of the upper lobe though its exact distribution was not ascertained in dissection. All the other structures were normal with the exception of the orifice of the coronary sinus which is located on the same side of the Eustachian valve as the inferior vena cava.



One case. Communication between a pulmonary vein and the portal vein by a branch perforating the diaphragm and going to the hilum of the liver in a child of 15 days.

Arnold, in Poirier & Charpy's *Traité d'anatomie humaine*, 1901, t. 2.

Such anomalies of the pulmonary veins have been explained by Brown ('13), on the basis of an anastomosis between the capillary plexuses in the embryo. He followed out the development in the domestic cat and supplemented this with the work of A. M. Miller on the chick.

In cat embryos of 4.5 mm., Brown describes a net-like capillary plexus in the mesenchyme surrounding the whole length of the intestinal tract. This plexus, which he designates the "splanchnic plexus" (Fig. 1), anastomoses freely with the adjacent veins of the systemic circulation. The cephalic part of the plexus anastomoses with the capillaries around the aorta, and with the precardinal and segmental veins; the caudal part, with the omphalo-mesenteric and post-cardinal veins. In addition to these communications there are two constant connections with the venous end of the heart, a cephalic or pulmonary, and a caudal or postcaval.

As the pulmonary anlage grows out from the intestinal tract it pushes before it the surrounding part of the splanchnic plexus. The capillaries of the two sides fuse into a common stem at the ventral pole of the anlage. This common stem, the anlage of the pulmonary vein, proceeds ventrally and somewhat caudally, to open into the sinus venosus, between and slightly dorsal to the ducts of Cuvier.

Flint (1907) takes the opposite view for the formation of the pulmonary vein. In the pig embryo he describes it as growing out from the sinus venosus and passing dorsally through the dorsal mesocardium to the pulmonary anlage. There it anastomoses with the plexus around the pulmonary anlage and the intestinal tract, though how this is accomplished he does not show.

Likewise, Federow (1910) describes the pulmonary vein as an outgrowth of the dorsal wall of the sinus venosus, for the amphibian, reptile, bird and mammal. He describes the cavity of the sinus as evaginating into a proliferation of the endothelium on the posterior wall of the sinus venosus, and at a later stage as connecting with the capillaries around the pulmonary anlage.

The splanchnic plexus, described by Brown, forms longitudinal drainage lines along the lateral and dorsal sides of the intestinal tract. At the level at which the sinusoids of the liver are forming, branches of the lateral longitudinal drainage lines fuse in the median plane into a single vessel, which passes cephalad through the dorsal mesocardium to the sinus venosus. This opens into the caudal part of the sinus venosus between the omphalo-mesenteric veins opposite the opening of the vein from the pulmonary anlage. At a somewhat later stage Brown recognizes in this the anlage of the hepatic and suprahepatic portions of the postcava.

This point seems to be somewhat confused. The hepatic and suprahepatic portions of the postcava or inferior vena cava, as described by Sabin (1915) for the pig, are derived from the

omphalo-mesenteric veins and certain hepatic sinusoids. This is the case for man also, as described by His (quoted by Mall, 1905). However, though Brown may have confused the development of the inferior vena cava, the communication between the splanchnic plexus and inferior vena cava would still hold good. Where the inferior vena cava—the portion from the mesial cardinal veins—curves ventralward toward the liver, Sabin (1915) describes a branch passing forward into the mesentery in the same dorsal position, to anastomose with the esophageal plexus just below the bifurcation of the trachea. On the left side a similar branch passes forward from the point of union of the two mesial cardinal veins to anastomose with the esophageal plexus.

These various anastomoses explain the anomalies of the pulmonary vein, being for the most part the persistence and an enlargement of one of these several communications which are found in the embryo and which ordinarily atrophy. The persistence of the communication between the pulmonary vein and the precardinal veins by way of the splanchnic plexus would explain the communication between an adult pulmonary vein and the innominate veins or the superior vena cava. Likewise, the persistence of the connection between the pulmonary vein and the esophageal plexus, and its connection with the developing inferior vena cava, would account for such a condition as was found in the several cases cited, where one of the pulmonary veins opened into the inferior vena cava. With the enlargement of one of the bronchial veins whose development is observed in slightly later stages, the connection between the pulmonary vein and the azygos or hemiazygos will be understood. The anastomosis between the splanchnic plexus and the omphalo-mesenteric veins is probably the cause of the few cases reported in which there was a communication between the pulmonary and portal systems. As the common stem from which the pulmonary veins develop is absorbed by the sinus venosus, its arrest at any stage would lead to a variation in the number of pulmonary veins found in the adult.

Brown shows how the pulmonary vein, which in an embryo 4.5 mm. long opens into the sinus venosus in the median plane, finally comes to empty into the left auricle. Between this and the 5 to 6 mm. stage a change takes place in the position of the sinus venosus in relation to the left auricle so that the orifice of the pulmonary vein opens to the left of the left sinus valve. The sinus moves caudalward and its lower portion shifts to the right side. The right duct of Cuvier is short and empties into the right cornu of the sinus; the left duct is longer and passes caudalward and to the right, to empty into the left cornu which joins the left part of the right cornu. The two cornua then open into the caudal and right aspect of the common auricle by a single orifice. With the subsequent formation of the right and left valves of the sinus, the orifice of the pulmonary vein, which has kept its relatively median position in the cephalic part of the sinus, comes to lie between the left valve of the sinus and the atrial septum (septum superius or primum) which is beginning to develop.

At a slightly later stage (6.5 to 7 mm.), the orifice of the pulmonary vein attains its permanent position in the left

auricle. This is brought about by changes which divide the heart into its several compartments. The cephalic part of the right valve of the sinus and the septum spurium, shift to the left and fuse with the atrial septum. The left valve of the sinus also moves to the left, its cephalic portion uniting with the dorso-caudal portion of the atrial septum. The orifice of the pulmonary vein precedes the left valve of the sinus and passes in under the atrial septum. With the formation of the auricular septum, the orifice lies in the left auricle and thus the pulmonary vein attains its permanent position.

The plexus around the pulmonary anlage has also undergone accompanying changes. Ventrally it is drained by the pulmonary vein; dorsally, communication has been established with the azygos and the hemiazygos by way of the plexus around the esophagus. This communication represents the future bronchial veins. The broncho-pulmonary anastomoses in the lung bud itself are apparent. The communication between the pulmonary plexus and the inferior vena cava by way of the esophageal plexus is only temporary. With further development, the plexus surrounding the pulmonary anlage loses its connection with the esophageal plexus and subsequently with the systemic veins, except for the bronchial veins and for occasional small veins.

In the two cases under consideration in which the upper left pulmonary vein empties into the left innominate, in terms of the above explanation, we have a persistence of the connection between the pulmonary plexus and the precardinal vein. In the one case which was completely dissected it was a persistence of that portion of the precardinal which ordinarily becomes the left oblique vein of the heart. It will be noted from the description that this was lacking in the adult. In the third case in which the upper vein of the right side emptied into the superior vena cava, the anomaly was likewise due to the persistence of the connection between the embryonic pulmonary plexus and the precardinal vein of the right side. Why we do not get a persistence of this embryonic condition more often is impossible to explain. According to Thoma (Mall, 1905) we find that ultimately it is something inherent in the tissues themselves which determines the development of the capillaries. Anything further than this would be mere conjecture.

## SUMMARY

The common pulmonary vein develops from the communication between the plexus surrounding the intestinal tract, designated by Brown as the "splanchnic plexus," and the sinus venosus. As to whether the vein is an outgrowth of the sinus venosus or whether it is derived from the plexus which is pushed forward by the developing lung bud is still a matter of dispute. The ventral and caudal portion of the plexus surrounding the lung bud is drained by the common pulmonary vein; the dorsal and cephalic portion is drained into the azygos and the hemiazygos by the future bronchial veins. The orifice of the common pulmonary vein, accompanying the unequal growth of the two halves of the sinus and auricle, empties into the sinus to the left of the left valve. The orifice precedes the shift of the left valve of the sinus to fuse with the atrial septum, passes under the latter and with the formation of the interauricular septum, empties into the left auricle.

The splanchnic plexus is connected with the adjacent capillaries and veins of the systemic and portal systems. The persistence and enlargement of any of these embryonic connections explains the various anomalies that have been found in the pulmonary veins. An investigation is now under way which it is hoped will clear up the few confused points and will show these conditions to be similar in the human embryo.

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## THE RELATION OF THE SUPPLYING OVARY TO THE CAUSATION OF SEX

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"The problem of the causation of sex in mankind has always been a fascinating one, and only recently it has been described as 'on the borderland of the insoluble.'"

The above paragraph is quoted from the preface to the first edition of "The Causation of Sex in Man," by E. Rumley Dawson of London, the second edition of which has recently been published in this country by Paul B. Hoeber, New York.

The principal theory advanced therein is that "the supplying ovary is in reality the essential factor in the causation of sex." This theory is so simple in its conception and so contradictory to the conclusions of recent investigators that it invites criticism.

From a careful consideration of the theories heretofore advanced concerning the causation of sex, the conviction is

obtained that sex is determined either in the germ-cells as such, or in the ovum shortly after the fusion of the male and female elements, but before segmentation occurs. The fact that in all mammalia single ovum twins are invariably of the same sex is alone sufficient proof that sex must be determined before segmentation has progressed, for this condition can result only when the first division of the fertilized egg has been so complete that two new cells are formed in which independent segmentation then proceeds. With this conviction it is not difficult to understand that all investigation of the problem, to be of value, must be based upon the study of the differences in the physiology of the reproductive organs of male and female, or upon the study of the physiology of the unsegmented fertilized ovum.

The reproductive organs of the two sexes differ so radically in function that it was not illogical that Schenk (1897) should have advanced the theory that the sex of the offspring could be influenced by the general physiology of one parent, and was determined by the state of nutrition of the female at the time of conception. In view of the occurrence of double ovum twins of different sexes, as Dawson says, the probability of such an influence is extremely unlikely. If we study the investigations which have been made upon the special physiology of the sex glands, we find that Doncaster (1914) has shown that certain species have both male and female ova, each type capable of developing by parthenogenesis; whereas, quite to the contrary, the work of Wilson (1906), Stevens (1906), Morgan (1913), and others show that in other species the sex-determining factor is present in the spermatozoa alone. In view of the evidence advanced by these workers concerning the influence in lower animals of the female element on the one hand and of the male element on the other, it seems probable that sex is determined in man before fusion of the elements. Further investigation may, however, show that one or the other element has a sex-determining property which is activated after fusion. If this should be shown it is evident that the causative factor of sex is present only in the fertilized unsegmented ovum.

It has been appreciated from earliest times that any theory of the causation of sex should be based upon physiological study. The necessity of this is realized by Dawson, and his theory depends upon the physiology of ovulation. Although termed a new theory, in its consideration one is reminded, in fact by Dawson himself, of similar theories previously advanced, particularly those of Hencke (1786) and Millot (1816). According to these male babies result from the union of ova from the right ovary with spermatozoa from the right testicle, while the union of ova and spermatozoa from the left-sided organs produces female children. The theory set forth by Dawson, that "a male foetus is due to the fertilization of an ovum that came from the right ovary, and a female foetus is due to the fertilization of an ovum that came from the left ovary," differs from this older one only in that "the spermatozoa do not influence sex at all." This principal theory is supplemented by another stating that the ovaries usually and normally ovulate alternately at an interval which can be deter-

mined in every woman by the length of her menstrual cycle. From these two premises Dawson deduces rules for "forecasting or predicting the sex of the unborn child, and on the determination or production of either sex at will."

Such a theory as that embodied in the first of these premises must be proven in two ways: First, by the demonstration of differences either in the ovaries or in the ova; and second, by clinical evidence.

Dawson interprets the slightly larger size of the right ovary as indicative of a special physiology for each ovary and, although histology teaches us that the tissue of the two ovaries is identical, he states that the ova in the right ovary differ from those in the left. He further attempts to prove this by reminding us that the ova of different mammalia and different races when fertilized produce only their kind, although the ova themselves do not differ in their known structure. He ascribes this "sexifying" factor to an ultra-microscopic or to a chemical property. That there may be differences in the ova of the two ovaries cannot be denied, but such differences can only be proven by work similar to that of Doncaster. Moreover, in the absence of parthenogenesis in mammalia, the chromosome theory of the causation of sex in man, advanced by Morgan and based upon the studies of von Winiwarter (1912), seems to indicate that such differences in human ova as claimed by Dawson, even if they exist, cannot be accepted as factors determining sex.

Clinically, Dawson attempts to prove that sex is determined by the ovary supplying the ovum by giving records of his own patients and by reference to cases in the literature, and, in addition thereto, by analogy from similar occurrences in domestic animals.

By direct observation of the ovaries during pregnancy or shortly after its termination the location of the corpus luteum of pregnancy can usually be ascertained. Only when this is seen macroscopically or microscopically, however, are we justified in concluding which ovary supplied the ovum fertilized. With the exception of those cases of pregnancy following the removal of an ovary, the examples given by Dawson are supposedly based upon such observations made at operation or post-mortem examination.

His cases are classified in certain obvious groups, each of which demands short comment.

*Group A (Chapter VIII).—*Cases of single intrauterine pregnancies can be used as conclusive proof of the theory without comment, provided the proper observations upon the location of the corpus luteum and the sex of the child have been made. In this group, also, would naturally fall cases of intrauterine multiple pregnancies. Instances of single ovum twins of known sex in which the corpus luteum is demonstrable are acceptable; while instances of double ovum twins are of doubtful value as confirmatory evidence. In the latter group there are six possible combinations of the location of the corpora lutea and the sex of the twins: (1) Different sexes with two corpora lutea in either ovary; (2) different sexes with a single corpus luteum in each ovary; (3) same sex with a corpus luteum in each ovary; (4) different sexes



with a corpus luteum in each ovary; (5) same sex with two corpora lutea in either ovary; (6) same sex with a single corpus luteum in either ovary. The possible occurrence of any one or all of the first three of these combinations is completely ignored by Dawson, who must have realized that such cases convincingly refute the claim that the right ovary alone supplies boys, and the left alone supplies girls. Instances of the fourth combination are apparently explained by him as being the few exceptions to "usual and normal unilateral ovulation." Instances of the fifth and sixth combinations are of value in confirmation of the theory only if the corpora lutea are demonstrated and the sex of the children known.

A careful study of the examples given by Dawson reveals but nine cases in this group of uncomplicated intrauterine pregnancies. Eight of these are single pregnancies, while the ninth falls into Group 5 of the double ovum twin combinations. In but three of the cases of single pregnancies is the presence of a right-sided corpus luteum in association with a male child demonstrated, while, in the other two cases of male children the location of the corpus luteum is inferred. In the other three single pregnancies he attempts to show the left-sided origin of female children, but in only one of them is the presence of the corpus luteum actually demonstrated. The case of twin pregnancy is cited twice in the book (Tufnell's case, pp. 63 and 134) and would be acceptable, were it not for the fact that the sex of one child is not given.

*Group B* (Chapter IX).—Cases of extrauterine pregnancy usually terminate, spontaneously or by operation, at such an early period that the sex of the fœtus cannot be discerned and, therefore, most cases given in the literature cannot be accepted in proof of the theory. Some of the cases cited by Dawson fail in their purpose because of this defect. Forty-nine of his cases of extrauterine pregnancy given cannot be accepted as conclusive proof because in none of them is the actual presence of the corpus luteum demonstrated. The evidence advanced that the tube involved in an ectopic gestation indicates that the corpus luteum of pregnancy is in the corresponding ovary cannot be accepted in view of the acknowledged frequency of the so-called migration of the ovum. None of the cases cited in this group meets both the requirements essential to prove the theory.

*Group C* (Chapter X).—It would seem that those cases of pregnancy following the removal of one ovary, which are advanced by Dawson in this chapter, would prove conclusively the first premise of his theory. Seventeen such instances, four of the pregnancies being in one woman, are cited. One of the lot, being a tubal pregnancy, is open to the objections applying to Group B. Other reviewers of this book have based adverse criticism, according to Dawson, upon instances of children of both sexes being born after the removal of an ovary, as well as upon instances of boys being born after a right oophorectomy or girls being born after the left ovary had been removed. Dawson replies in answer to such criticism: "In these few exceptional cases who shall say some true ovarian tissue had not been left behind? or that there

was no accessory ovarian tissue?" This argument is equally as effective in criticism of the cases cited by Dawson as in criticism of the cases adduced by his reviewers.

*Group D* (Chapter XI).—Instances of pregnancies in one horn of abnormal uteri should logically be placed in Group A along with those of intrauterine pregnancies, but, inasmuch as Dawson groups such cases separately, the cases given in this chapter will be considered separately. A total of 16 such cases, including seven repeated pregnancies, are cited as examples in favor of the theory. In 12 of these, including the repeated pregnancies, the location of the corpus luteum is not given, but is inferred from the horn or half of the uterus containing the pregnancy. This is the same method he used to determine the location of the corpus luteum in the cases of extrauterine pregnancy, and, as stated above, cannot be considered accurate because of the possibility of migration of the ovum. In two cases the location of the corpus luteum is again inferred from its absence in the only ovary examined. In another case the sex of the child is not stated, while the last case is given only by the title and not described. For those reasons, none of the cases cited in this chapter can be accepted.

This criticism of the examples given by Dawson is rather severe, for it shows that but four of his examples, a very small percentage of the total, are acceptable in proof of his theory. It is made, however, for the reason that any clinical argument against his theory must be based upon cases similar to those used by him and at the same time free from the objections that might make them liable to such criticism.

At the suggestion of Dr. Williams, the records of some 17,500 deliveries occurring in the Obstetrical Clinic of The Johns Hopkins Hospital from September, 1896, to March, 1918, were searched for suitable cases by which the principal theory advanced by Dawson could be tested. All those cases in which the location of the corpus luteum was actually demonstrated at Cæsarean section, at laparotomy for therapeutic abortion, at laparotomy within two weeks after delivery, or at post-mortem examination, and in which there was no question as to the sex of the child, were tabulated. While observations made at Cæsarean sections had frequently shown that male children were not always derived from the right ovary, and that female children were not always derived from the left ovary, the results obtained in Table I were rather surprising.

In all, 75 suitable observations were made on 70 women, five women each having two pregnancies. It is remarkable that the corpus luteum was found to be in the right ovary in 38 of the cases, and in the left ovary in 37 of the cases: an equal division. In 68 per cent, or in 26, of the cases in which the corpus luteum was located in the right ovary the child was male, while in the remaining 32 per cent, or 12 cases, the child was female. On the other hand, in 57 per cent, or in 21, of the cases in which the corpus luteum was located in the left ovary the child was male, while in the remaining 43 per cent, or in 16, of these cases the child was female. When we analyze the 75 cases from the standpoint of sex the result is more striking. In our series there were 47 male and 28 female children; 63 per cent and 37 per cent respectively.

For the 47 males the corpus luteum was found in the right ovary in 26, or 55 per cent, and in the left ovary in 21, or 45 per cent; while for the 28 females the corpus luteum was found in the right ovary in 12, or 43 per cent, and in the left ovary in 16, or 57 per cent.

From these figures it is evident that Dawson's theory cannot be correct, and, considering that the majority of the children in this series of cases are male, it is also clear that babies of either sex result in about equal numbers from the fertilization of an ovum from either ovary. Furthermore, one is led to say that clinical evidence shows that the determination of sex is probably not due to any factor present in the unfertilized ovum.

It is not considered necessary to quote in detail the histories of all the cases, but the five instances of repeated pregnancies in the same women are worthy of special consideration.

*Pregnancies of Rachel J.*—J. H. H. 5687. Delivered by conservative Cesarean section on December 18, 1912, of a female child at term. Corpus luteum observed in the left ovary. J. H. H. 7027. Again delivered by conservative Cesarean section on March 29, 1915, of a female child at term. Corpus luteum again observed in the left ovary.

*Pregnancies of Scala F.*—J. H. H. 6549. Delivered by conservative Cesarean section on April 24, 1914, of a female child at term. Corpus luteum observed in the left ovary. J. H. H. 8955. Again delivered by conservative Cesarean section on December 10, 1917, of a female child at term. Corpus luteum again observed in the left ovary.

*Pregnancies of Mary L.*—J. H. H. 7122. Delivered by conservative Cesarean section on March 24, 1915, of a male child at term. Corpus luteum observed in the right ovary. J. H. H. 8666. Again delivered by conservative Cesarean section on July 15, 1917, of a male child at term. Corpus luteum again observed in the right ovary.

*Pregnancies of Minnie F.*—J. H. H. 7291. Delivered by conservative Cesarean section on July 2, 1915, of a male child at term. Corpus luteum observed in the right ovary. J. H. H. 8537. Again delivered by conservative Cesarean section on May 12, 1917, of a male child at term. Corpus luteum again observed in the right ovary.

*Pregnancies of Delia D.*—J. H. H. 7276. Delivered by conservative Cesarean section on July 1, 1915, of a female child at the ninth lunar month of gestation. Corpus luteum observed in the right ovary. J. H. H. 8242. Again delivered by conservative Cesarean section on December 14, 1916, of a female child at term. Corpus luteum observed in the left ovary.

The first eight of these pregnancies seem to uphold Dawson's theory. The last woman, however, had two pregnancies resulting in females with the corpus luteum of the first pregnancy on the right side and that of the second pregnancy on the left. These two pregnancies, therefore, completely contradict the conclusion, which might be based upon the first eight pregnancies, that "the essential factor in the causation of sex" is connected with the supplying ovary.

In addition to these 75 observations, one instance of double ovum twin pregnancy was noted, in which a single corpus luteum only was demonstrated.

*Pregnancy of Barbara D.*—J. H. H. 8131. The patient, who was pregnant for the fourth time, died from eclampsia before delivery. Autopsy (4896) showed that the uterus contained a double ovum twin pregnancy of about nine lunar months' duration. The

twins, both female, were definitely double ovum in origin; the placenta being attached to opposite sides of the uterus and two complete sets of membranes being demonstrated. But only one corpus luteum of pregnancy could be found on macroscopical or microscopical examination of the ovaries (Obstet. Path., C. W. 1479), and that was in the right ovary.

If any inference can be drawn from a single case, this is offered as evidence against the left-sided origin of female children.

In view of the evidence afforded above of the failure of Dawson's theory concerning the predominating influence of the ovary in the causation of sex in beings, it hardly seems necessary to take notice of conditions in domestic animals. Furthermore, in criticizing the work of Doncaster, Dawson discounts any such proof in favor of his theory, as follows: "We have, however, no evidence that what occurs in the polytocous animals . . . must equally apply to monotocous woman."

Being based upon one false premise it is evident that Dawson's rules for the prediction of sex cannot be accurate; but, for the sake of making this criticism more destructive, the second premise will also be shown to be fallacious.

The second premise upon which Dawson bases his rules is that the ovaries ovulate alternately. It has been supposed, but never proven, that this is the case. Dawson, in attempting to prove it, reviews the literature upon the subject and, without making any contribution thereto, takes the supposition for granted. This premise is, therefore, based upon questionable evidence. In addition, he states in explanation of the greater number of male births: ". . . so that more ova are produced by the large right or male ovary than by the opposite or smaller left ovary." One is tempted to ask how more ova can come from the right ovary, other than in multiple pregnancies, if this ovary ovulates alternately and, therefore, just as frequently as the left. The argument advanced to prove the alternating action of the ovaries hardly deserves comment, for it is based mainly upon evidence afforded by symptoms at the time of menstruation, which, because of its subjective nature, cannot be considered trustworthy.

With the first premise false and the second based upon uncertain evidence, Dawson's rules for the determination of the sex of the unborn child cannot be accurate. In spite of this, however, and especially as Dawson claims success in 97 per cent of all attempts, it seems best that his rules should be applied to a group of cases.

In their most simple form these rules are: First, as menstruation is usually accepted as a sign of ovulation, any woman who menstruates normally every 28 days will ovulate 13 times yearly. Second, as the ovaries normally and usually ovulate alternately and unilaterally, ova will be discharged at alternate months from opposite ovaries. If, therefore, the date of the birth of a full-term child is known, and, consequently, the month determined in which its ovary functionated according to the rule, by proper calculation the sex of a child resulting from impregnation in any subsequent menstrual period can be foretold.

This simple formula advanced by Dawson was applied to all pregnancies in the women who furnished the basis for Table I,

TABLE I

Name of patient	House service number	Pregnancy		Date of delivery	Male children Corpus luteum		Female children Corpus luteum		Pathological numbers		
		Order	Duration		Right	Left	Right	Left	Autopsy	Service	
CÆSAREAN SECTIONS											
Annie J.	1420	3d	Term	Mar. 2 03	+	..	..	..	..	C. W. 585½	
Rachel J.	5687	3d	Term	Dec. 18 12	..	..	..	+	..	..	
	7027	4th	Term	Mar. 29 15	..	..	..	+	..	..	
Clara J.	5709	1st	9 mos.	Nov. 30 12	+	..	..	..	3825	C. W. 1216	
Florence S.	6184	1st	Term	Sept. 1 13	+	..	..	..	..	..	
Evelyn Y.	6241	1st	7 mos.	Nov. 3 13	..	..	..	+	..	..	
Dora S.	6313	1st	Term	Dec. 3 13	+	..	..	..	..	..	
Seala F.	6549	7th	Term	Apr. 21 14	..	..	..	+	..	..	
	8955	8th	Term	Dec. 10 17	..	..	..	+	..	..	
Emma C.	6847	2d	Term	Oct. 31 14	..	+	..	..	..	C. W. 1331	
Hattie J.	6893	3d	Term	Jan. 3 15	..	..	..	..	..	..	
Carrie S.	6971	2d	Term	Jan. 6 15	..	+	..	..	..	..	
Annie H.	7072	1st	Term	Feb. 27 15	+	..	..	..	..	C. W. 1366	
Mary L.	7122	1st	Term	Mar. 24 15	+	..	..	..	..	..	
	8666	2d	Term	July 15 17	+	..	..	..	..	..	
Henrietta R.	7145	5th	Term	Apr. 9 15	..	..	..	..	..	C. W. 1377	
Minnie F.	7291	3d	Term	July 2 15	+	..	..	..	..	..	
	8537	4th	Term	May 12 17	+	..	..	..	..	..	
Delia D.	7276	2d	9 mos.	July 1 15	..	..	+	..	..	..	
	8212	3d	Term	Dec. 14 16	..	..	..	+	..	..	
Esther H.	7705	3d	Term	Apr. 8 16	..	+	..	..	..	C. W. 1457	
Ruth S.	7928	1st	Term	June 22 16	..	..	..	..	..	..	
Marcella H.	8137	3d	Term	Oct. 21 16	..	+	..	..	..	C. W. 1480	
Eliza D.	8196	3d	Term	Nov. 21 16	..	..	..	..	..	..	
Ida G.	8486	1st	Term	Apr. 10 17	..	+	..	..	..	..	
Marie B.	8753	3d	Term	Aug. 28 17	+	..	..	..	..	..	
Daisy J.	8820	3d	Term	Sept. 23 17	+	..	..	..	..	..	
Sueie D.	8826	4th	Term	Oct. 16 17	+	..	..	..	5334	C. W. 1540	
Rose F.	8861	1st	Term	Oct. 18 17	..	+	..	..	..	..	
Mary F.	9008	7th	Term	Jan. 3 18	..	..	..	..	..	..	
Marie L.	9083	2d	Term	Feb. 8 18	..	..	..	+	..	..	
Edwina R.	9084	2d	Term	Feb. 15 18	..	..	..	+	..	..	
Lula W.	9092	3d	6 mos.	Feb. 14 18	..	+	..	..	..	..	
Lizzie L.	9115	2d	8 mos.	Feb. 15 18	+	..	..	..	..	..	
ABDOMINAL THERAPEUTIC ABORTIONS											
Bessie H.	6926	5th	4 mos.	Dec. 12 14	..	+	..	..	..	..	
Wanda Z.	7870	6th	4 mos.	May 31 16	..	..	..	+	..	C. W. 1466	
Alice L.	8717	?	4 mos.	Aug. 10 17	..	..	..	+	..	C. W. 1533	
Christina G.	8986	?	3 mos.	Dec. 22 17	..	..	..	+	..	..	
EXPLORATORY LAPAROTOMIES											
Elsie R.	5386	5th	Term	Apr. 30 12	+ (operated and died 2 weeks post partum)			..	3730	C. W. 1147	
Florence W.	6694	4th	Term	Aug. 17 14	(op. 2 weeks postpartum) +			..	..	C. W. 1314	
Genieve G. W.	7570	3d	Term	Dec. 1 15	+ (operated at delivery)			..	..	C. W. 1433	
Tenie O.	7692	9th	Term	Feb. 9 16	(operated at delivery) +			..	..	C. W. 1450	
AUTOPSIES											
Emma P.	9	1st	Term	Oct. 28 96	+	(died 2 days postpartum)	..	..	Lost	C. W. 505	
Margaret B.	27	6th	Term	Feb. 16 97	+	(died 5 days postpartum)	..	..	912	..	
Anna Y.	372	?	Term	Feb. 10 99	+	(died 26 days postpartum)	..	..	1304	C. W. 549	
Eliza C.	460	13th	Term	July 10 99	(died 1 day postpartum)	+	..	..	1389	C. W. 550	
Gussie H.	866	?	7 mos.	Apr. 15 01	(died 1 day postpartum)	..	+	..	1715	..	
Eliza D.	1040	11th	Term	Jan. 15 02	(died 1 day at delivery)	..	+	..	1850	C. W. 583	
Mary S.	1177	1st	7 mos.	May 29 02	(died 2 hrs. postpartum)	+	..	..	1934	C. W. 597	
Elizabeth F.	1297	9th	Term	Oct. 5 02	..	(died few hrs. postpartum)	..	..	2004	..	
Eleanor J.	2158	1st	Term	July 5 05	(died 4 days postpartum)	+	..	..	2566	..	
Annie H.	2568	6th	Term	May 3 06	(died at delivery)	+	..	..	2718	..	
May H.	2610	1st	Term	June 21 56	(died few hrs. postpartum)	+	..	..	2737	..	
Mary F.	2828	3d	6 mos.	Nov. 11 06	..	(died 34 days postpartum)	..	..	2813	..	
Rosetta B.	4116	2d	Term	Nov. 10 09	+	(died 5 days postpartum)	..	..	3294	..	
Nora D.	4155	1st	Term	Oct. 26 09	+	(died 5 days postpartum)	..	..	3288	..	
Mary S.	4203	3d	Term	Nov. 29 09	+	(died 3 days postpartum)	..	..	3303	C. W. 1030	
Margaret F.	4205	11th	Term	Dec. 3 09	(died 5 hours postpartum)	+	..	..	3305	C. W. 1031	
Hallie G.	4346	1st	Term	Mar. 18 10	+	(died 4 days postpartum)	..	..	3356	..	
Georgie P.	5250	1st	Term	Feb. 23 12	..	(died 3 days postpartum)	..	..	3697	..	
Annie C.	5394	1st	Term	May 5 12	..	(died 5 days postpartum)	..	..	3726	..	
Margaret S.	5911	1st	Term	Mar. 30 13	+	(died 4 days postpartum)	..	..	3900	..	
Mary M.	6093	1st	9 mos.	July 11 13	(died 3 days postpartum)	+	..	..	3963	..	
Ruth B.	6730	9th	Term	Aug. 8 14	(died 4 days postpartum)	+	..	..	4170	..	
Edna P.	7390	1st	9 mos.	Aug. 27 15	..	(died 10 days postpartum)	..	..	4116	..	
Rose J.	7483	4th	7 mos.	Oct. 14 15	+	(died 17 days postpartum)	..	..	4190	..	
Alverta M.	7666	?	Term	Dec. 25 15	..	(died 6 days postpartum)	..	..	4546	C. W. 1443	
Ada G.	7902	1st	Term	June 5 19	(died at delivery)	+	..	..	4711	..	
Elizabeth B.	8287	3d	Term	Jan. 25 17	..	(died 4 days postpartum)	..	..	5014	..	
Lillian T.	8302	2d	Term	Jan. 27 17	(died 8 days postpartum)	+	..	..	5024	..	
Vivian C.	8405	1st	3 mos.	Mar. 25 17	..	(died during pregnancy)	..	..	5077	C. W. 1506	
Viola W.	8570	3d	Term	June 17 17	+	(died 2 days postpartum)	..	..	5184	C. W. 1519	
Francis H.	8797½	7th	7 mos.	Sept. 30 17	(died 5 days postpartum)	+	..	..	5319	C. W. 1539	
Lena L.	8844	5th	3 mos.	Oct. 26 17	..	(died during pregnancy)	..	..	5339	C. W. 1541	
Kathleen S.	9000	2d	9 mos.	Jan. 4 18	(died 12 days postpartum)	+	..	..	5417	..	
Totals.....75	75	Corpus luteum right....38			26	21	12	16			
Corpus luteum left.....37					47		28				



TABLE II

Name of patient	Service number	Order of pregnancy	Date of delivery	Sex of child	Calculated sex	Confirms theory	Refutes theory
Annie J.....	J. H. H. 751	2d	Oct. 2 00	Female	..	..	..
	J. H. H. 1420	3d	Mar. 2 03	Male	Male	+	..
Annie H.....	J. H. H. 1057	5th	Jan. 14 04	Male	..	..	..
	J. H. H. 2568	6th	May 3 06	Female	Male	..	+
Eather H.....	J. H. H. 2237	2d	Aug. 12 05	Female	..	..	..
	J. H. H. 7705	3d	Apr. 8 16	Male	Female	..	+
Rosetta B.....	J. H. H. 2739	1st	Dec. 4 06	Male	..	..	..
	J. H. H. 4116	2d	Nov. 10 09	Male	Male	+	..
Margaret F.....	J. H. H. 2900	10th	Feb. 20 07	Female	..	..	..
	J. H. H. 4205	11th	Dec. 3 09	Female	Male	..	+
Rachel J.....	J. H. H. 5687	3d	Dec. 18 12	Female	..	..	..
	J. H. H. 7027	4th	Mar. 29 15	Female	Female	+	..
Seala F.....	J. H. H. 6549	7th	Apr. 21 14	Female	..	..	..
	J. H. H. 8955	8th	Dec. 10 17	Female	Male	..	+
Lillian T.....	J. H. H. 6864	1st	Nov. 6 14	Male	..	..	..
	J. H. H. 8302	2d	Jan. 27 17	Female	Female	+	..
Mary L.....	J. H. H. 7112	1st	Mar. 24 15	Male	..	..	..
	J. H. H. 8666	2d	July 15 17	Male	Male	+	..
Edwina R.....	J. H. H. 7071	1st	Aug. 8 15	Male	..	..	..
	J. H. H. 9084	2d	Feb. 15 18	Female	Female	+	..
Elizabeth B.....	O. O. S. 3965	1st	Oct. 23 08	Female	..	..	..
	O. O. S. 4527	2d	Jan. 22 10	Male	Male	+	..
	J. H. H. 8287	3d	Jan. 25 17	Male	Female	..	+
Viola W.....	O. O. S. 5287	1st	Oct. 12 11	Female	..	..	..
	O. O. S. 5996	2d	May 24 13	Female	Female	+	..
	J. H. H. 8570	3d	June 17 17	Male	Male	+	..
Carrie S.....	J. H. H. 6283	1st	Nov. 18 13	Male	..	..	..
	J. H. H. 6971	2d	Jan. 6 15	Male	Female	..	+
	J. H. H. 8332	3d	Jan. 29 17	Female	Male	..	+
Ruth B.....	O. O. S. 1515	6th	Mar. 10 02	Male	..	..	..
	O. O. S. 2927	7th	May 27 06	Male	Male	+	..
	O. O. S. 5031	8th	Mar. 12 11	Male	Female	..	+
	J. H. H. 6730	9th	Aug. 8 14	Female	Female	+	..
Henrietta R.....	J. H. H. 2728	2d	Nov. 27 06	Male	..	..	..
	J. H. H. 3894	3d	May 10 09	Female	Male	..	+
	J. H. H. 5398	4th	July 23 12	Male	Female	..	+
	J. H. H. 7145	5th	Apr. 9 15	Male	Female	..	+
Hattie J.....	J. H. H. 5142	1st	Dec. 18 11	Male	..	..	..
	J. H. H. 6156	2d	Aug. 12 13	Male	Female	..	+
	J. H. H. 6893	3d	Jan. 3 15	Male	Male	+	..
	J. H. H. 8303	4th	Dec. 27 16	Male	Female	..	+
Susie D.....	J. H. H. 5354	1st	June 18 12	Male	..	..	..
	J. H. H. 6075	2d	Jan. 7 15	Female	Female	+	..
	J. H. H. 7835	3d	Apr. 29 16	Female	Female	+	..
	J. H. H. 8826	4th	Oct. 16 17	Male	Female	..	+
Minnie F.....	J. H. H. 5898	1st	Mar. 22 13	Female	..	..	..
	J. H. H. 6460	2d	Feb. 25 14	Female	Female	+	..
	J. H. H. 7291	3d	July 2 15	Male	Female	..	+
	J. H. H. 8537	4th	May 12 17	Male	Female	..	+
Elsie R.....	J. H. H. 2657	1st	July 26 06	Male	..	..	..
	O. O. S. 3734	2d	Apr. 6 08	Male	Male	+	..
	J. H. H. 3972	3d	June 3 09	Male	Female	..	+
	O. O. S. 4922	4th	Dec. 17 10	Female	Female	+	..
	J. H. H. 5386	5th	Apr. 30 12	Male	Male	+	..
Florence W.....	O. O. S. 4252	1st	June 9 09	Female	..	..	..
	O. O. S. 4780	2d	Aug. 20 10	Female	Male	..	+
	J. H. H. 5393	3d	May 4 12	Female	Female	+	..
	J. H. H. 6694	4th	Aug. 17 14	Female	Male	..	+
	O. O. S. 7306	5th	Jan. 31 16	Female	Female	+	..
	O. O. S. 7962	6th	May 27 17	Male	Female	..	+
Totals..... 20	60			60	40	20	20

employing only repeated full-term pregnancies occurring in women whose menstrual cycle was 28 days. Twenty women were found who had had 60 pregnancies. In 40 of these the sex of the children subsequent to the first child was calculated and compared with the sex of the child as noted at delivery. The results of this comparison are given in Table II and show that Dawson's rule was accurate in but 50 per cent, or in 20, of the cases; a percentage that is in keeping with the laws of probability and chance.

#### CONCLUSIONS

The conclusions reached from this consideration of Dawson's theory that the supplying ovary is the essential factor in the causation of sex, and from the application of his rules to a group of cases free of any objections are:

1. The supplying ovary has no influence upon the sex of the child.
2. Male and female children result in about equal numbers from the fertilization of ova from either ovary.

3. The causation of sex is probably not due to any factor in the unfertilized ovum.

4. The "chromosome theory" must be considered the only explanation of the causation of sex at present acceptable.

5. The sex of an unborn child cannot be foretold, nor can either sex be produced at will, by any rules known at present.

## REFERENCES

References to the authorities quoted in this article and to the other literature upon this subject will be found in the footnotes in Dawson's book, "The Causation of Sex in Man," Hoeber, 1917, and in J. Whitridge Williams' "Obstetrics," IV Ed., Appleton, 1917, pp. 170-172.

## THE PISTON ACTION OF THE VERTEBRAL COLUMN DEVELOPED IN CERTAIN TYPES OF CRANIAL FRACTURES

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The casualties developed upon a modern aviation field occasionally present conditions of great scientific interest. Neither time nor occasion would warrant a discussion or even a tabulation of the types afforded in this interesting and highly important service. A brief note upon the following case, observed at a former post, would seem to be worthy of record:

An airship, of the usual training type, made an ordinary "take off." This was promptly (indeed prematurely) followed by a "zoom" at such an acute angle that, lacking the needful velocity, the ship crashed to earth. The pilot (second cockpit) was practically uninjured; the mechanic (forward cockpit) was killed.

For the present occasion, the only injury to be discussed was that sustained by the cranium. Bleeding from the nose and ears, in moderate quantity, was in evidence; the vertical diameter of the head (in proportion to the general contour) seemed somewhat shortened. There were no surface lesions of head, face, or neck, of pertinent significance. When the scalp was removed a curvilinear fracture beginning at the left frontal eminence was found; this tended inferiorly and disappeared, beneath the peeled scalp, at approximately the lateral margin of the left supraorbital ridge. When the calvarium was lifted, the brain surface was found to be engorged, with numerous subdural hemorrhages; the brain mass was perceptibly less firm than usual, and markedly flattened out when laid upon the table. On removal it was noted that the spinal cord had been severed at approximately its junction with the medulla. The distal stump lay posteriorly upon the occipital bone.

The frontal fracture (*vid. ante*) was found to have entered the left anterior fossa at A, to have proceeded posteriorly and medially, dividing and subdividing until, having circumscribed the foramen magnum, it ceased to be visible or palpable at B in the right occipital fossa.

It is a matter of regret that obedience to service regulation regarding autopsies forbade a thorough orientation of the cranial base, the face, and the vertebral column. It is highly probable that further careful study would have exhibited matters of substantial scientific value.

All cranial fractures are of surgical interest, but the feature that makes this basal fracture worthy of record is the fact that

the entire basal mass, circumscribed by the fracture, was driven superiorly within the cranial cavity to an extent varying at different points, from  $\frac{1}{8}$ " to  $\frac{3}{4}$ ". The figure fails to exhibit the notably serrated margins; nor would time permit an at-

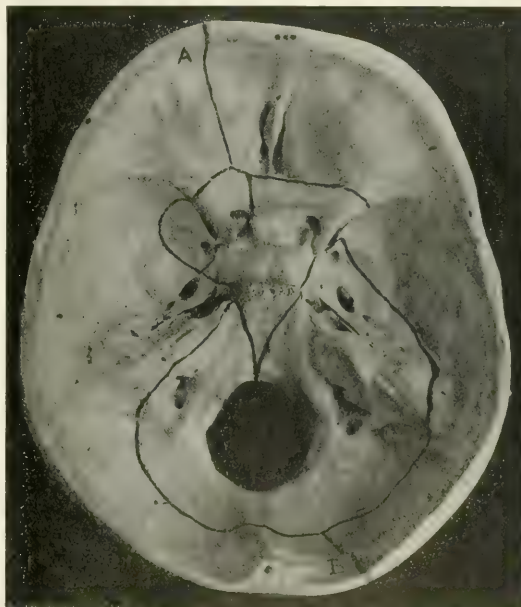


FIG. 1.—Exhibiting tracing of basal fracture of skull. In order to portray the extension of the fracture down to the foramen magnum, the skull has been considerably tilted. (Secured through the courtesy of Prof. Augustus G. Pohlman, professor of anatomy, Medical Department, St. Louis University.)

tempt to portray the damage executed by numerous lanceolate spicules and massive fragments that lacerated and lifted the dura in radiating planes.

The question might well be raised, What caused this enormous trauma of the cranial base? As noted above, the surface markings of scalp, face, and neck were devoid of significance.

"Fracture by contrecoup" would doubtless have sufficed as an explanation in the past, not so to-day. The following seems to be most worthy of credence:

The unchecked "nose-down" fall of an airship is highly destructive, owing to the great disproportion that exists between the heavy motor and the light fuselage. The terrific impact usually telescopes the former into the latter. It is well known that the forward cockpit is more liable to destruction than the second. The victim, in this instance, seated in the forward cockpit sustained the crushing drive of the motor upon his vertex (transmitted either through the anterior rim of the forward cockpit, or more probably through the instrument board). The tremendous upward thrust of the motor on the vertex was met by the counterthrust of the fuselage and equipment, plus the weight of the two men, strapped in their seats. It is fairly obvious that the vertebral column, acting as a piston, drove before it the cranial base, to invade the cranial cavity, as above noted.

This eighteenth century hypothesis, of the French, has been discredited in the light of studies upon cranial elasticity and cranial meridians by Aran, von Bruns, Messner, Hermann, von Wahl, Hilton, Félizet, and Cushing. Of particular interest is the observation of Hilton, regarding one anteroposterior and two transverse osseous buttress-arches, in relation to well-known areas of structural weakness.

Had this fracture been developed by the more usual types of vertical impact it might have been anticipated that a fair conformation to the structural configuration of the cranium (*conf. footnote*) would follow. But even the strong counterthrust of the vertebral column exerted upon the cranial base would hardly suffice to account for the fracture variations exhibited. If, however, consideration be given to the manifest probability that a marked flexion of the head upon the thorax was developed, thus permitting a substantial supplementary counterthrust to be exerted through the chin and the temporomandibular articulations, orientation of the variant fissures will prove less difficult.

This piston action of the vertebral column merits consideration in the differential study of cranial traumata, developed by severe vertical impact. But it is an open question whether this piston action of the vertebral column, in explanation of certain types of cranial fracture, has received the consideration that it merits. Well digested evidence, based upon further experimental, operative, and autopsy procedures, should prove valuable.

It but remains to add that in all probability similar basal fractures, developed by similar factors, in similar environment, will arise more or less constantly in the Aviation Service, and transform an abstract surgical problem into one of vitally practical significance.

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FIG. 1. Illustrating stricture of right ureter due to gunshot injury. The plate is reversed. Symptoms began 8 years after injury. Note stricture just below the pelvic brim, and the slight dilatation of the ureter after 3 months of rather severe kidney symptoms. Bladder urine normal on infection. Symptoms entirely relieved by three dilations.



FIG. 2. Same patient as illustrated by FIG. 1, the catheter being withdrawn until the way-bells, located in the bend, the tip of the catheter, has obstructed in the upper structure of the iliac gland region. Note slight dilatation of the ureter between this structure and the lower stricture in the broad ligament region.



FIG. 3. Mrs. M., aged 54 years. Referred by Dr. T. B. Johnson of Frederick. Right kidney. Illustrates slight dilatation of pelvic ureter above a stricture in the broad ligament region, and a wider dilatation of the ureter, hydronephrosis, pelo-lapso, and kinks in the upper ureter, due to a stricture in the iliac gland region. A way-catheter obstructing in a kink. Severe attack of grippe and sinusitis in May, 1916. In January, 1917, severe attack of pain in the upper right flank which was attributed to be either cystitis or appendicitis, because the urine was reported as normal. In December, 1916, another severe attack of pain in the upper right flank which was attributed to be either cystitis or appendicitis, because the urine was reported as normal. In December, 1916, another severe attack of sinusitis and in the following 2 months 3 severe attacks of pain in the upper right flank. When seen February 24, 1917, the patient was having pain in the lumbar and iliac regions and drag in both sides of the pelvis. Temperature 101.5, pulse 100, and some blood under frequency. The urine contained a considerable number of leukocytes, erythrocytes, and a heavy mass of albumin. West has history and these findings a diagnosis was made of bilateral ureteral stricture. Irrigation showed mild triple stricture in the pelvis, the left kidney holding its size and yielding urine with a few leukocytes but no infection. The right kidney held 2 1/2 oz. and yielded urine with a considerable number of leukocytes, some blood and a cloudy bacillus infection. The patient showed much improvement after a few dilations of the strictures during March. She returned home with the idea of coming back for catheterizations, but in May she was taken with marked symptoms of nephritis, including a purpura and hemorrhage from both ears. Her physician reported that there was no temperature elevation, a blood pressure of 190/105, and secretion of an almost negligible quantity of uric acid. Death from pneumonia in June.



FIG. 4. Mrs. R., 24 years of age. Referred by Dr. T. B. Johnson, 29, 1917, and Dr. T. B. Johnson, 29, 1918. Symptoms typical of chronic pyelitis, beginning in 1917, with severe attacks of pain in the upper right flank, extending from the bladder, and causing a marked constipation, including a purpura, purpura, and sinusitis, renal thrombosis and ineffective attempts at stool. Urine port-wine color, with blood, many leukocytes, negative reaction. Symptoms relieved by three dilations. Right kidney holds 2 1/2 oz. composed of 1/2 of stricture, the rest of the kidney.



FIG. 6. Mrs. P., 60 years of age, referred by Dr. Harkness, Birmingham, Ala. Patient admitted to the Glenn Home and Laboratory May 28, 1917. Since April 5, 1917, four attacks of hematuria, each attack lasting four days. No pain, a slight uneasy feeling in the right flank during the attacks. Renal catheter entered right ureter only 3 to 4 cm. There was profuse hematuria at 12 c.c. There was no dilatation of ureters, no mass from the bladder. Report October 1, 1917, no further bleeding and no symptoms.



FIG. 7. Mrs. P., 60 years of age, referred by Dr. Harkness, Birmingham, Ala. Patient admitted to the Glenn Home and Laboratory May 28, 1917. Since April 5, 1917, four attacks of hematuria, each attack lasting four days. No pain, a slight uneasy feeling in the right flank during the attacks. Renal catheter entered right ureter only 3 to 4 cm. There was profuse hematuria at 12 c.c. There was no dilatation of ureters, no mass from the bladder. Report October 1, 1917, no further bleeding and no symptoms.



FIG. 8. Mrs. P., 60 years of age, referred by Dr. Harkness, Birmingham, Ala. Patient admitted to the Glenn Home and Laboratory May 28, 1917. Since April 5, 1917, four attacks of hematuria, each attack lasting four days. No pain, a slight uneasy feeling in the right flank during the attacks. Renal catheter entered right ureter only 3 to 4 cm. There was profuse hematuria at 12 c.c. There was no dilatation of ureters, no mass from the bladder. Report October 1, 1917, no further bleeding and no symptoms.



FIG. 9. Illustrates a case with almost impassable obstruction from below but in which the character of the obstruction was not typical. The patient had a long history of urinary tract disease. The obstruction was a thin-shaped band of adhesions suspending the sigmoid bowel to the posterior peritoneum. The adhesions probably followed a severe illness with typhoid fever during girlhood.





Fig. 9.—Same incision as illustrated in Fig. 8 after the operation of tying the sigmoid from the posterior peritoneum.



Fig. 10.—Plate should have been printed to show incision on right side. Mrs. L., aged 41 years, complained of pain in the lower right pelvis, through the hip and in the thigh since 16 years of age. Considered to be due to a fall across a fence. Also considered as female trouble because pain came only at the menstrual periods for the first few years. For the last 20 years the pain has come on at any time but is worse at the menstrual period. In the past year more pain in the right kidney region. Operated, J. H. H., March, 1914: Appendectomy and supracervical hysterectomy for pelvic inflammatory disease and fibroids. Before leaving, the patient told Dr. Watkins, the resident gynecologist, that he had failed to cut out her old pain low in the right leg. Mr. Associate, Dr. Verne, made the first examination for ureteral stricture, and the patient said she was sure he had discovered her trouble because she could scarcely use the right leg the day following his treatment. The kidney pelvis held but 5 c. c.; her symptoms were greatly improved after 5 treatments. She will probably need tonsillectomy.

Fig. 11a. Case 62. Dense bilateral strictures, ureters slightly dilated, kidney pelvis held only 4 to 5 c. c. Mrs. C., aged 42 years, referred by Dr. Thomas R. Brown because of attacks of pain in the right side like Dietl's crises, accompanied by leukocytes and erythrocytes in the urine. The patient had been operated upon 6 months previously, a suspension of the uterus, appendectomy, and repair of the outlet having been done and she was still complaining of the pain in the right side which had prompted her to seek relief in operation. She described this pain as a constant ache in the right kidney region, extending down the line of the right ureter. When standing or walking the pain was in the posterior flank. When lying down it was more anterior like a "stomach pressure." At all times there was a pain in the ureter region halfway between the kidney and the bony pelvis. Several kidney investigations in May, 1915, failed to discover the source of her trouble. In December, 1915, after becoming interested in ureteral stricture, a wax-bulb was added to the renal catheter and there was a definite hang on its withdrawal. In August, 1916, the patient began complaining of pain in the left side and a dense stricture was found on that side. The dilations have been carried on irregularly for 2 years and in the meantime the patient has had some abscessed teeth extracted and is now having treatment for infected tonsils and sinuses. She has improved in general health and does not require hypodermics of morphia except on rare occasions after treatment. Before the discovery of the strictures, she was getting somewhat dependent upon morphia to control the pain.



Fig. 11.—Mrs. H., aged 37 years, referred by Dr. J. C. Watson, W. J. Watson, M.D. Pain in the upper right abdomen for over 7 years. The gallbladder is a growing tumor in upper flank, at times in front, at times in back, at times in axillary line. Interfered with getting to sleep. Thinks she feels best when up and moving about. Alkaline, passed 4 stones ago. Recently, X-rays taken in Philadelphia for gall-stones; negative. Gastric analysis=hypo-acidity. Wassermann negative. History of rheumatic fever. X-rays of two crowned teeth show abscesses. Urine examination normal. Test for ureteral stricture, wax-bulb hangs at iliac gland region, and broad ligament region. Pain much relieved after the first examination, and a gain of 5 pounds in last weeks. Only 2 dilations necessary.



Fig. 11a.—Mrs. H., aged 37 years, referred by Dr. J. C. Watson, W. J. Watson, M.D. Pain in the upper right abdomen for over 7 years. The gallbladder is a growing tumor in upper flank, at times in front, at times in back, at times in axillary line. Interfered with getting to sleep. Thinks she feels best when up and moving about. Alkaline, passed 4 stones ago. Recently, X-rays taken in Philadelphia for gall-stones; negative. Gastric analysis=hypo-acidity. Wassermann negative. History of rheumatic fever. X-rays of two crowned teeth show abscesses. Urine examination normal. Test for ureteral stricture, wax-bulb hangs at iliac gland region, and broad ligament region. Pain much relieved after the first examination, and a gain of 5 pounds in last weeks. Only 2 dilations necessary.



FIG. 10. The same patient with food removed. The mass is seen in the upper part of the abdomen. The mass is large and rounded, and is surrounded by less dense tissue.



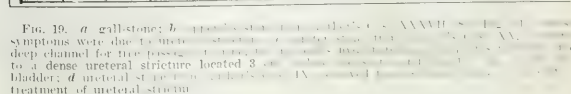
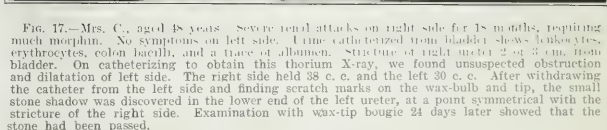
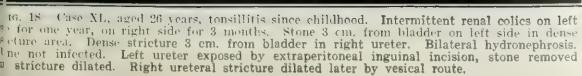
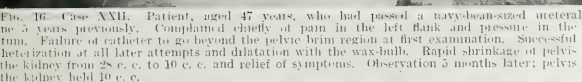
FIG. 11. Same mass as Fig. 10, showing slight indentation of the left border.



FIG. 12. The same patient with food removed. The mass is seen in the upper part of the abdomen. The mass is large and rounded, and is surrounded by less dense tissue. The mass is large and rounded, and is surrounded by less dense tissue.



FIG. 13. The same patient with food removed. The mass is seen in the upper part of the abdomen. The mass is large and rounded, and is surrounded by less dense tissue. The mass is large and rounded, and is surrounded by less dense tissue.







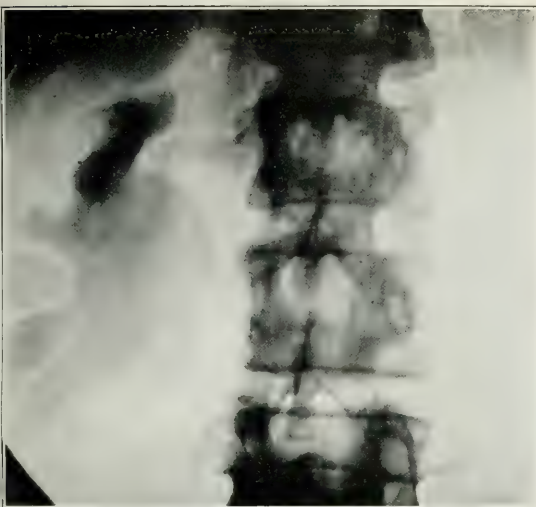


FIG. 24.—Case XLIX. Tonsillitis since early childhood. Left hydronephrosis attacks since 2 years of age. Destroyed left kidney removed in 1901, at age of 22 years. Hysterectomy for fibroids January, 1915. Convalescence marked by pyelitis attacks in right kidney. Intermittent lavage for 10 months often followed by severe pyelitis attacks. Pyelogram, Charlottesville, Va.: Right kidney pelvis holds 40 c.c.; ureteral stricture well dilated October, 1915; colon bacillus infection and all symptoms gone December, 1915.



FIG. 25. Miss H., Case 76, aged 11 years, referred by Dr. C. A. Woodward, Durham, N. C. For 5 years attacks of acute pyelitis in alternate kidneys accompanied by pain, chills, temperature ranging as high as 103° F., much bladder distress and frequency, and pus in the urine. Tonsillitis since infancy, the tonsils having been removed 1 year before my consultation. The diagnosis of probable bilateral ureteral stricture with secondary colon bacillus pyelitis was made on the foregoing history and examination with the wax bulb catheter, thorium pyelography, and culture taking confirmed the diagnosis. The illustration demonstrates the difficulty of introducing the proper amount of thorium in a child. It shows the rounded outline of the kidney pelvis with somewhat obliterated calyces and portions of the dilated ureters partially filled with thorium.



FIG. 26 illustrates the same case as Fig. 25, showing the low end of the left ureter at the site of stricture.



FIG. 27. Patient identical with Case 76. Left kidney removed 1901. Attacks of chills and a nocturnal fever ranging from 101° to 104° F. Right kidney removed 1905. Tonsils removed 1906. Left ureter removed 1907. Both ureters had adhered to the abdominal wall. After removal of the ureters in either side. After operation, the patient remained in bed for 4 months. After being discharged, the patient presented a history of recurrent attacks of pyelitis. Urine from each kidney showing colon bacillus infection. The patient remained in bed for four years until death from general debility.







FIG. 32.—Mrs. S., aged 29 years, referred by Dr. R. C. Fernald, Richmond. The right kidney had been removed one year previously for calculus. Patient complaining of pain in the left kidney region and low in the left pelvis, and passing thick, purulent urine, yielding colon bacillus culture. Dilatation of stricture 3 cm. above bladder and relief from pain. Repeated lavage failed to clear the urine. X-ray shows eroded character of pelvis outline. Search for tubercle bacilli; present in large numbers.

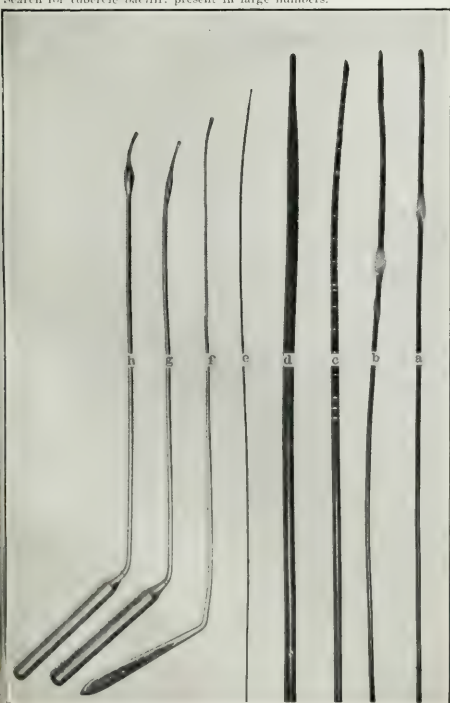


FIG. 33.—Set of ureteral catheters, etc., used by author, *a* blunt round-tip renal catheter with wax-bulb; *b* olive-tip renal catheter with large wax bulb, protected on either side with smaller bulb; *c* Garceau graduated whistle tip catheter; *d* flexible bougie (7 mm. diam.). Sizes vary from 3 to 10 mm., the smaller sizes being useful for dilating through the cystoscope from below, and the larger sizes for retrograde dilatation from above; *e* whalebone filiform (varying sizes are used through the cystoscope); *f* metal searcher with olive tip; *g* metal bulb dilator 3 mm. with curved olive tip; *h* metal bulb dilator 5 mm. with curved olive tip.

Spiral wax tip



FIG. 34.



FIG. 35.—Plate should have been made to show the shadow on the left side. Miss H., aged 40 years. Right nephrectomy for stone April, 1900. Consulted Dr. Kelly, May, 1914, for a constant pain in the left kidney region. Investigation of kidney and failure to find cause of the pain. Consulted author in June, 1914, and again in March, 1915, and no cause found in the urinary tract for the pain. Operation, J. H. H., March, 1915; hysterectomy for fibroids and left oophorectomy for "tender left ovary." Returned in October, 1915, with the same pain in the left kidney region, and examination showed definite stricture and a hydronephrosis of 18 c.c. This hydronephrosis increased to 32 c.c., while the patient was having repeated dilatations of the stricture. After removal of several abscessed teeth the dilatations gave permanent relief, with a shrinkage of the pelvis of the kidney to 10 c.c.



FIG. 36.—L. P., aged 11 years. Right nephrectomy for intermittent hydronephrosis attacks. These attacks began at 3 years of age, came three or four times a year. The attacks were suddenly and lasted from one hour to several days and then stopped suddenly. There was no fever, chills or hematuria. About the age of 10 years the patient was treated with catheters for 2 years and at 9 years of age the ureteral stricture in the broad ligament region. There were no attacks after the first dilatation. The patient was dismissed after 3 treatments. There had been throat trouble, once only, and enlarged, diseased tonsils, removed while the patient was under treatment.





FIG. 1.—Anat. No. 1188. Gyn. No. 20777. This photograph of the gross specimen shows very beautifully the chorionic villi protruding through the perforation in the posterior superior surface. The portion of tube and the area of endometrium removed are also clearly shown. (Photographed by Dr. Daniel Davis.)

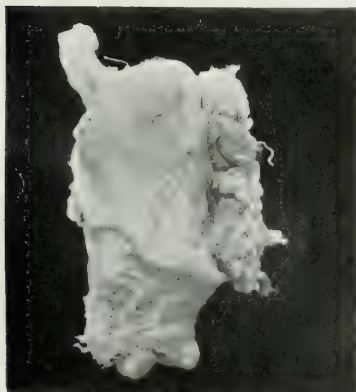


FIG. 2.—Anat. No. 1188. Gyn. No. 20777. Posterior view of the specimen showing projecting placental tissue, tube and endometrium. (Photograph loaned by Dep. of Anatomy.)

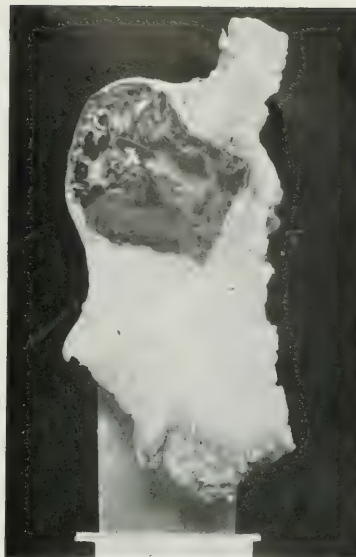


FIG. 3.—Anat. No. 1188. Gyn. No. 20777. (  $\times 2$ .) Longitudinal section through the specimen showing the gestation sac, uterine wall, endometrium and two cross-sections of the tube. (Photograph loaned by Dep. of Anatomy.)



FIG. 8.—Gyn. Path. No. 14277. Superior surface of the gross specimen. The opening into the gestation sac is clearly shown. The original blocks taken from the uterine cornu and tube can be seen. (Photographed by Dr. Daniel Davis.)





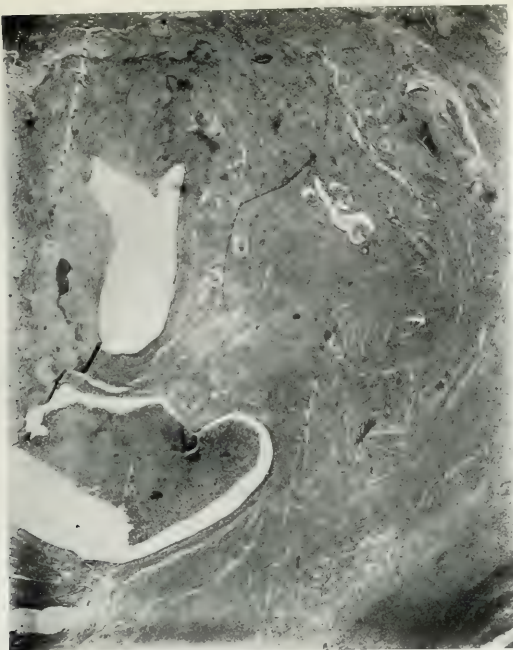


FIG. 4.—Gyn. Path. No. 14277. ( $\times 15$ .) Portion of the uterine cornu (cross-section) distal to the gestation sac, showing the interstitial portion of the tube and its relation to the three cavities described above. These cavities are much larger than the lumen of the tube. (Photograph by Hoffmann.)

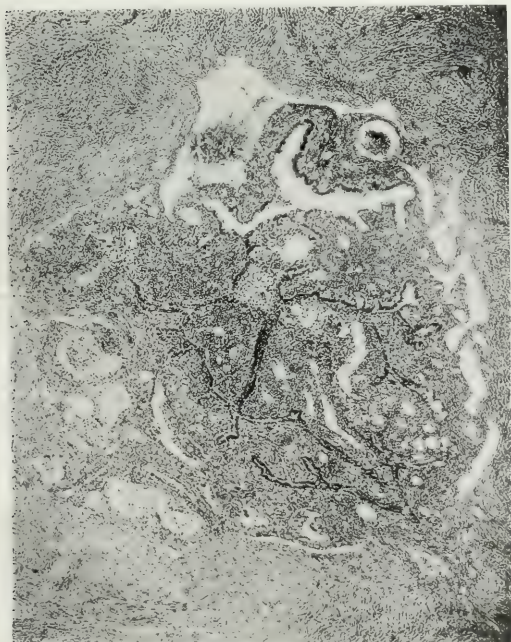


FIG. 5.—Anat. No. 1188. Gyn. No. 20777. ( $\times 35$ .) Section of tube proximal to the gestation sac. The strands of epithelium of the mucosa have been compressed by inflammatory changes until the lumen is almost obliterated. (Microphotograph by Hoffmann.)

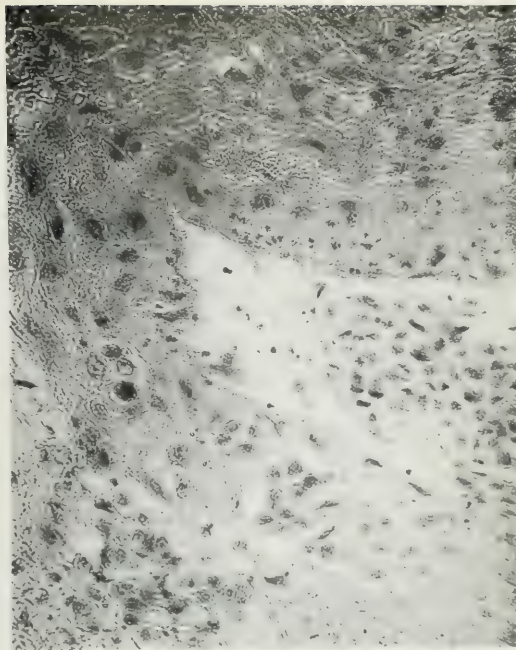


FIG. 6.—Anat. No. 1188. Gyn. No. 20777. ( $\times 115$ .) Syncytial invasion of tube wall and decidual reaction of tube. (Microphotograph by Hoffmann.)

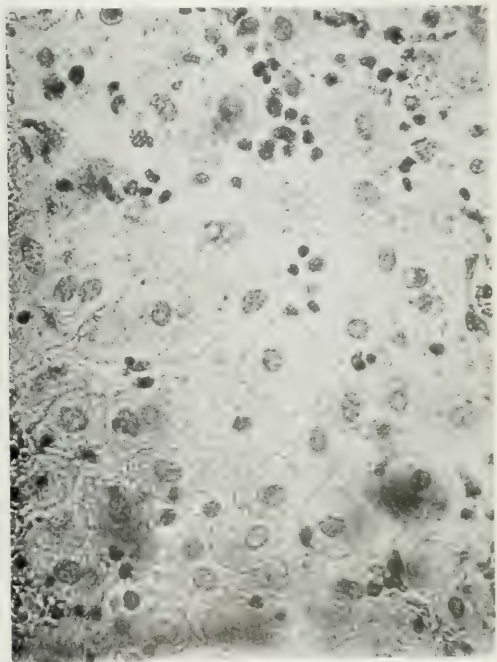


FIG. 7.—Anat. No. 1188. Gyn. No. 20777. ( $\times 300$ .) Decidual reaction of endometrium with leucocytic infiltration. (Microphotograph by Hoffmann.)







FIG. 1.



FIG. 2.

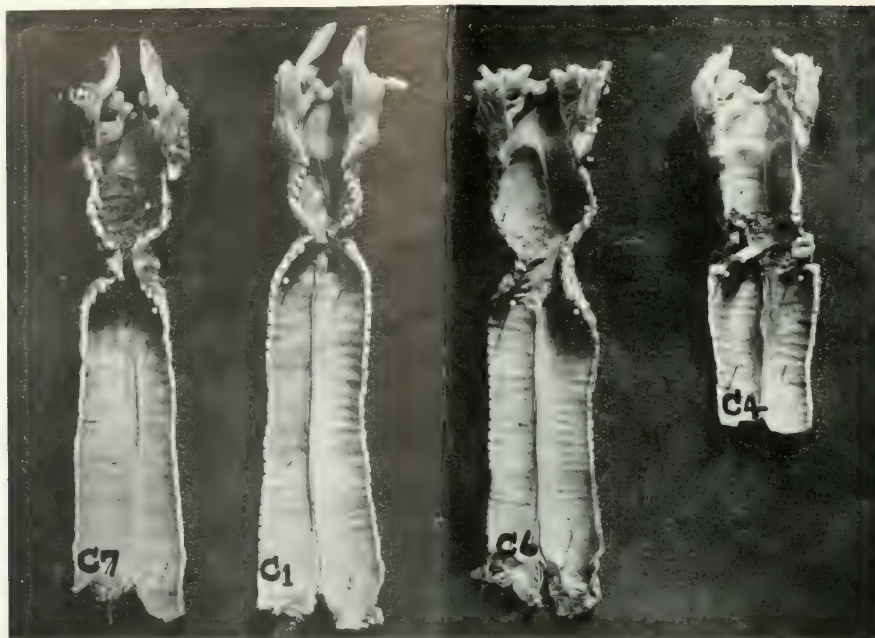


FIG. 3.

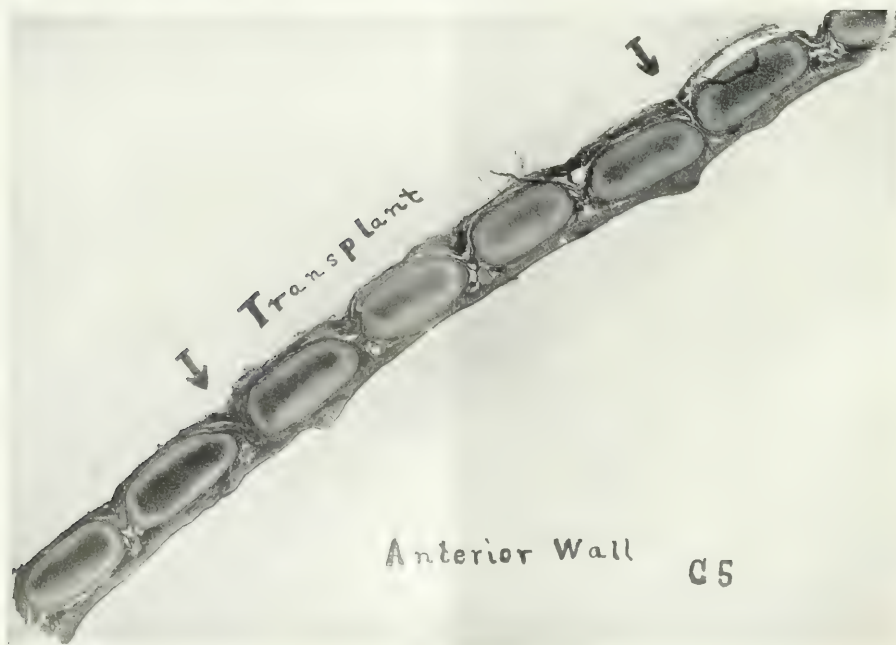


FIG. 4.

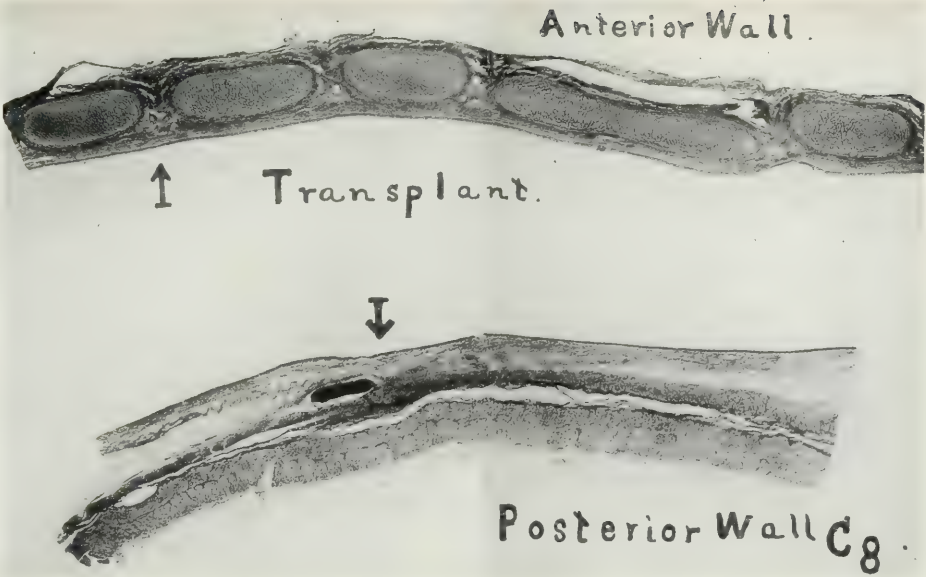


FIG. 5.

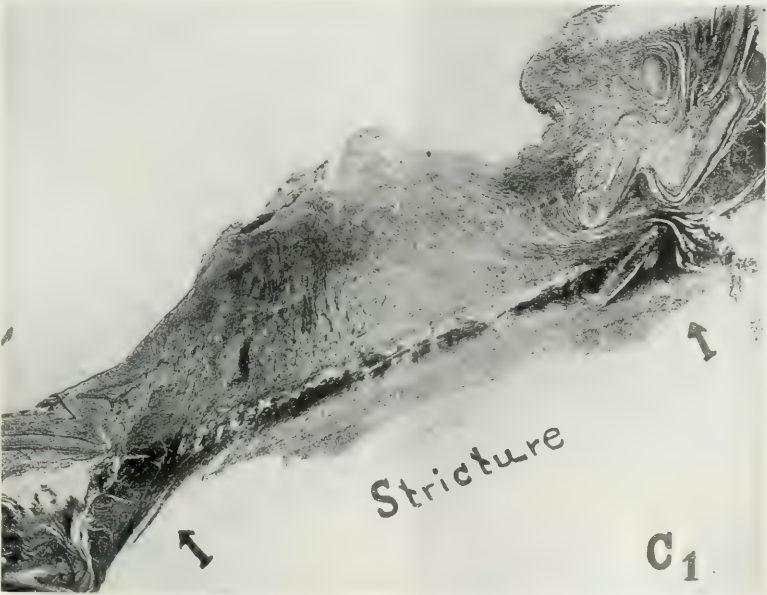


FIG. 6.







FIG. 4.—Photograph of the kidneys of dog 1. Specimens fixed in formalin. Duration of the right anastomosis two months and three days, of the left seven days. Both anastomoses are patent.



FIG. 5.—Photograph of the formalin-fixed specimen of dog 4. Duration of the right anastomosis two months, of the left five days. Both ureters are patent. There is no thrombosis. Note the hydronephrosis.





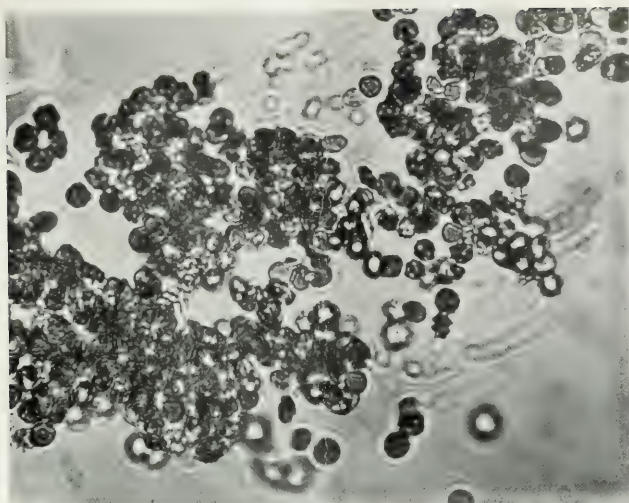


FIG. 1.

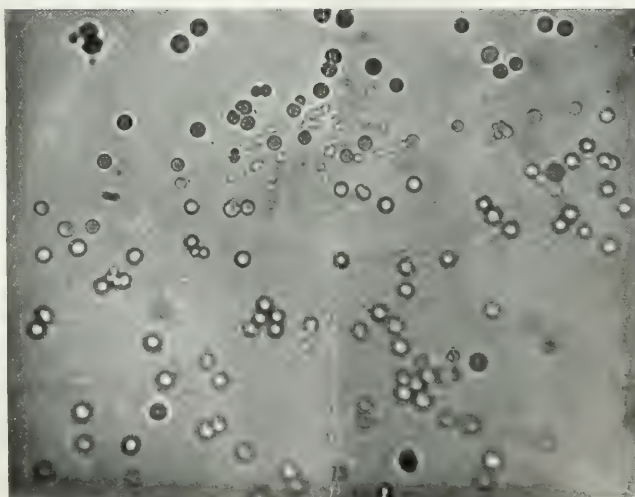


FIG. 2.



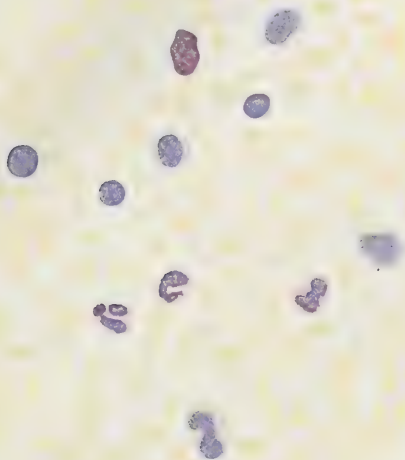


FIG. 1

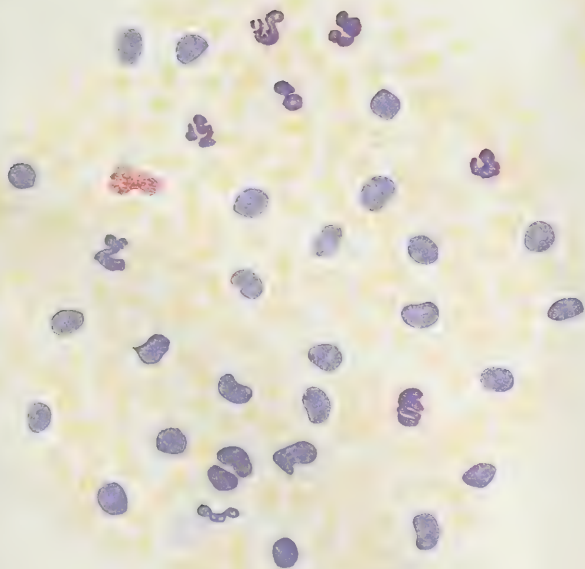
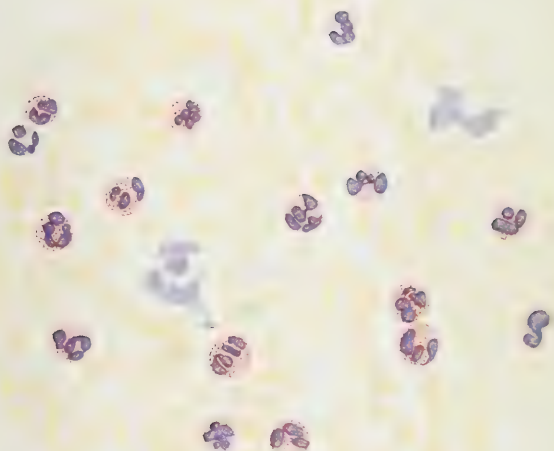


FIG. 2.







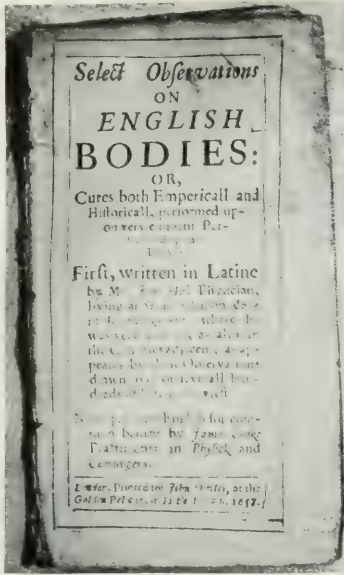


FIG. 1.



FIG. 2.

*Thos. Nash F. G. S.*

*P. J. Nash*

*Eliza Nash*

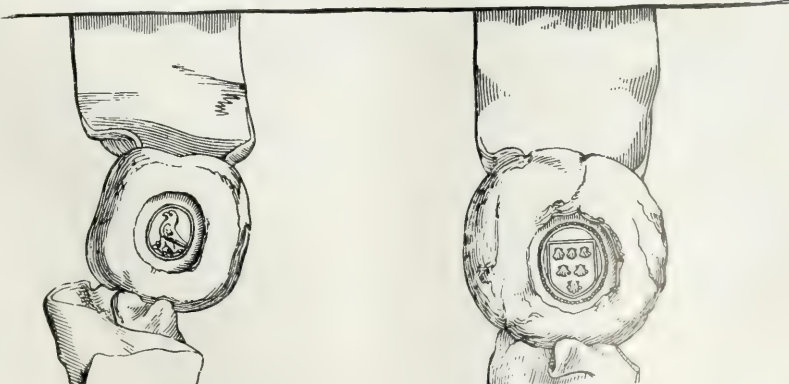


FIG. 3.







FIG. 1.—Left hand.



FIG. 2.—Right hand.



FIG. 3.

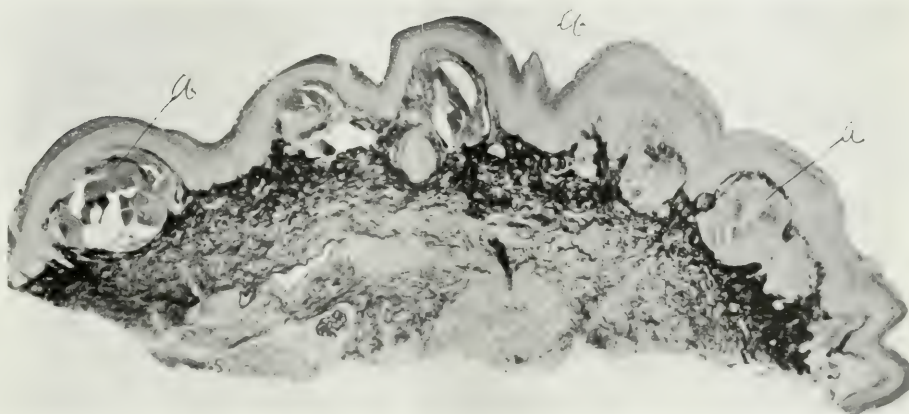


FIG. 4.—Weigert's elastic tissue stain, showing masses of colloid material in papillary layer of the cutis *a, a, a*.

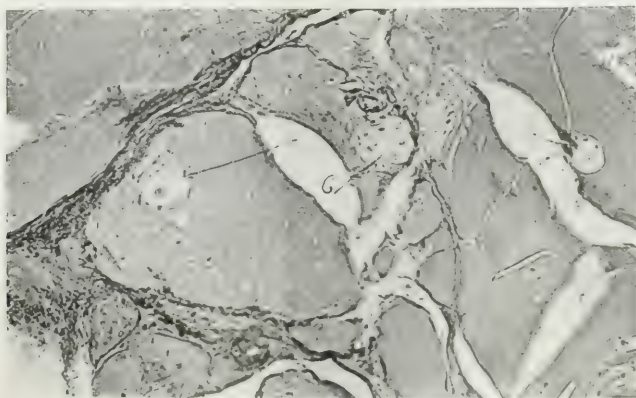


FIG. 5. Enlargement of small area within one of the colloid masses (fig. 4, *a*). *b*, Large cells with granular protoplasm. *c* shows gland-like arrangement of these cells.





FIG. 1.—Sarcoma arising from the endometrium of the uterus. Endometrium normal everywhere except at the left cornu where the growth is attached. Tubes and ovaries normal.

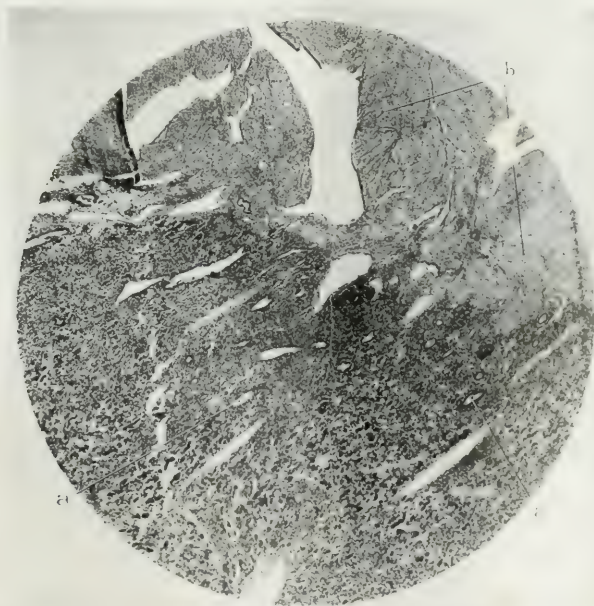


FIG. 2.—Low-power picture. In the upper part of the microphotograph we find normal uterine muscle. The junction of the mucosa with the muscle is sharply defined. The endometrium contains a few glands, but the greater part of the tissue is made up of large irregular cells of the sarcoma.





FIG. 3.—Low-power picture. The dark areas are sarcomatous and one can readily, even with the low power, make out large black masses of pigment in sarcoma cells. *a* marks an island of tumor cells surrounded by normal uterine muscle (*b*).

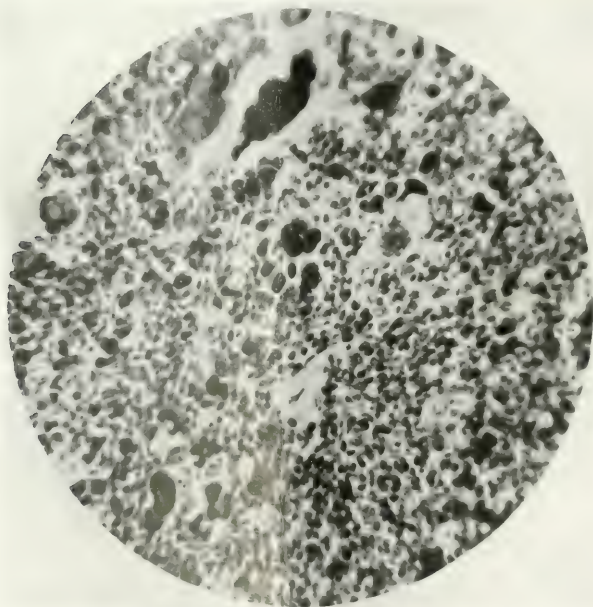


FIG. 4.—Characteristic appearance of the growth with the high power. The cells, as a whole, are fairly uniform and have uniform and deeply staining nuclei, but here and there are large irregular masses of pigment.

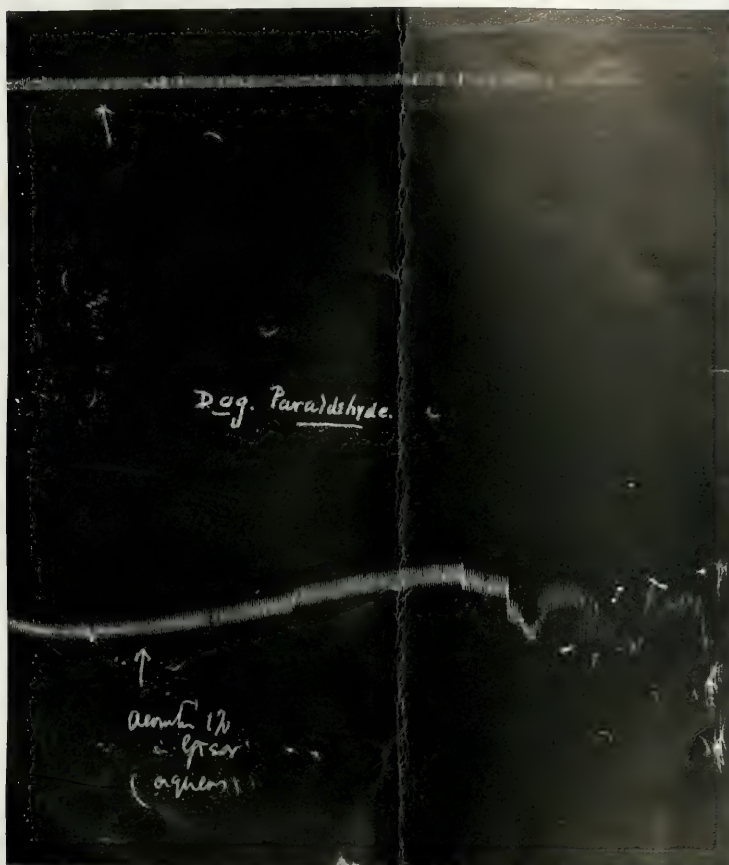


FIG. 1.—Dog. Paraldehyde Anesthesia. 1 per cent of Aqueous Solution of Aconitin HCl in left ear. Showing effect on heart and respiration.

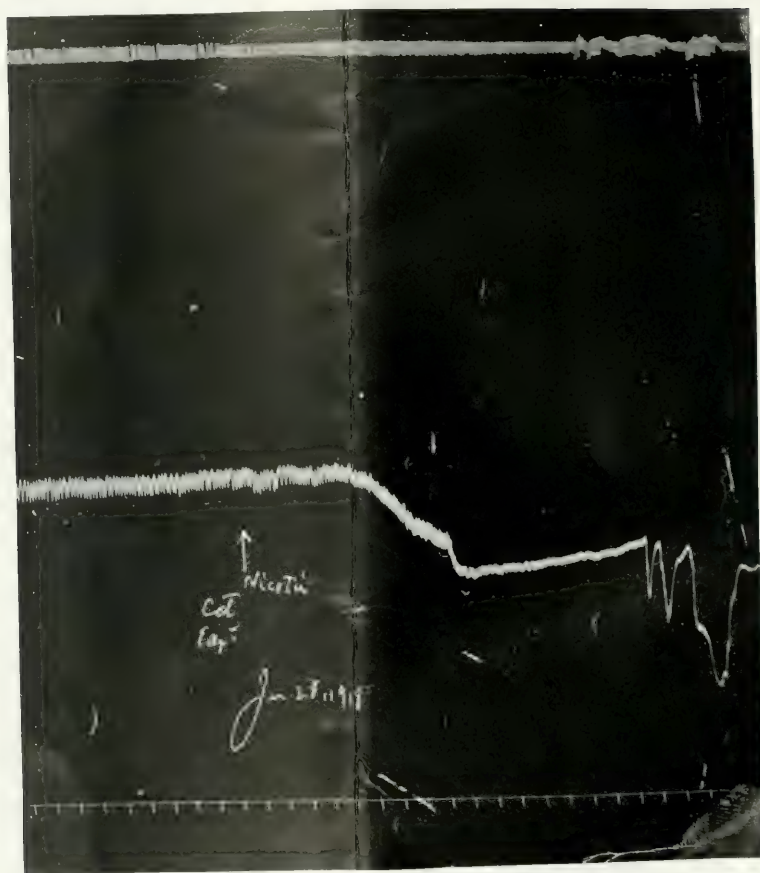


FIG. 2. Cat. Urethane Anesthesia. A few drops of Nicotin instilled into the ear produce death in 15 minutes.





FIG. 1.



FIG. 3.



FIG. 2





FIG. 1.—Patient on Admission.

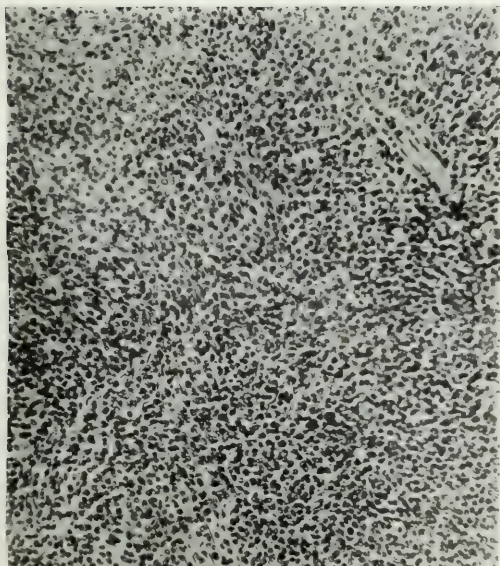


FIG. 2.—Microscopic Section of Stomach Tumor. Zeiss obj. AA, oc. 4. Haematoxylin and Eosin.

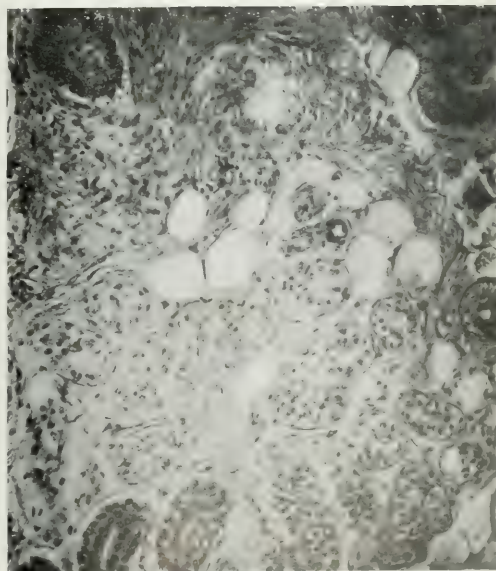


FIG. 3.—Microscopic Section of Face Tumor. Zeiss obj. AA, oc. 4. Haematoxylin and Eosin.







FIG. 1.



FIG. 2.

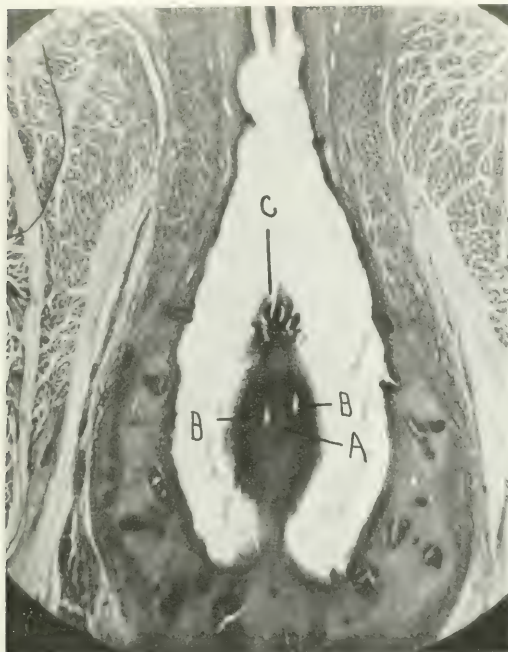


FIG. 3.

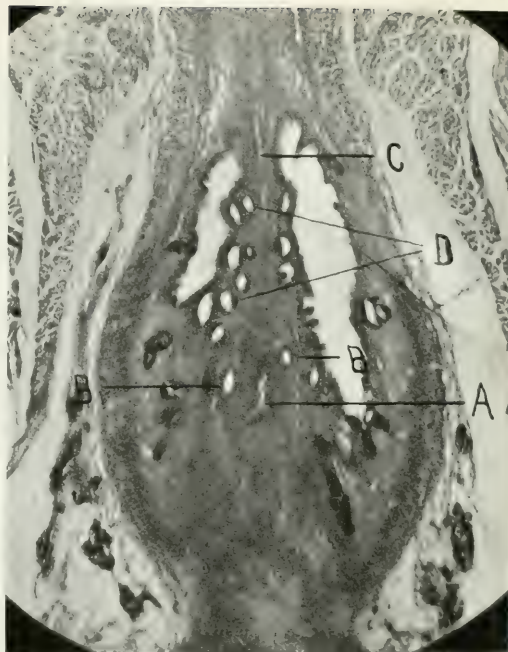


FIG. 4.



FIG. 5.

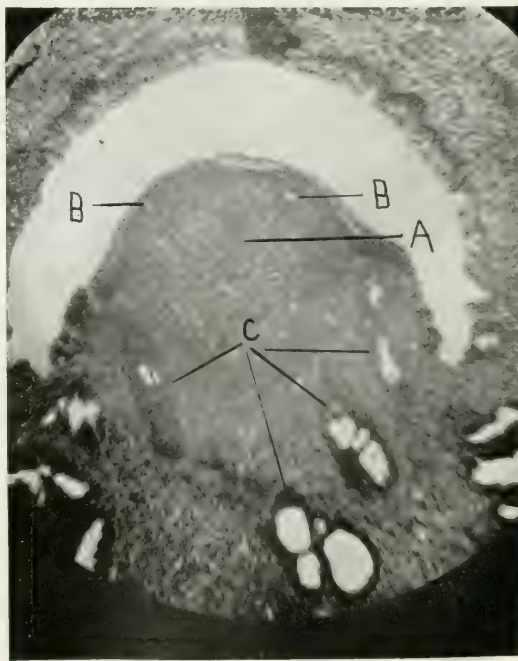


FIG. 6.



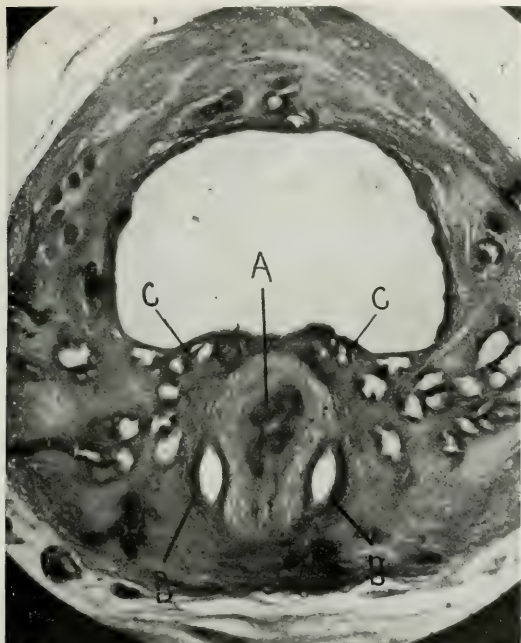


FIG. 7.

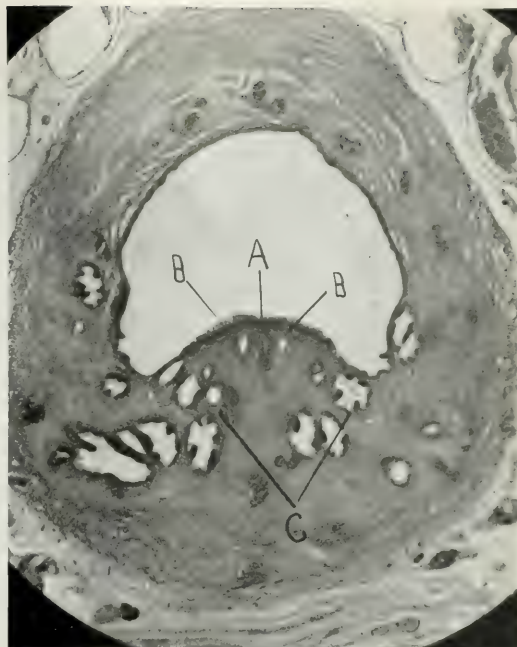


FIG. 8.

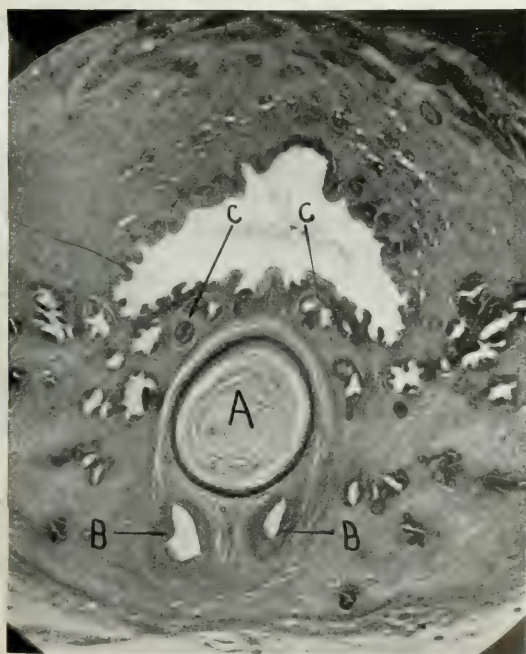


FIG. 9.

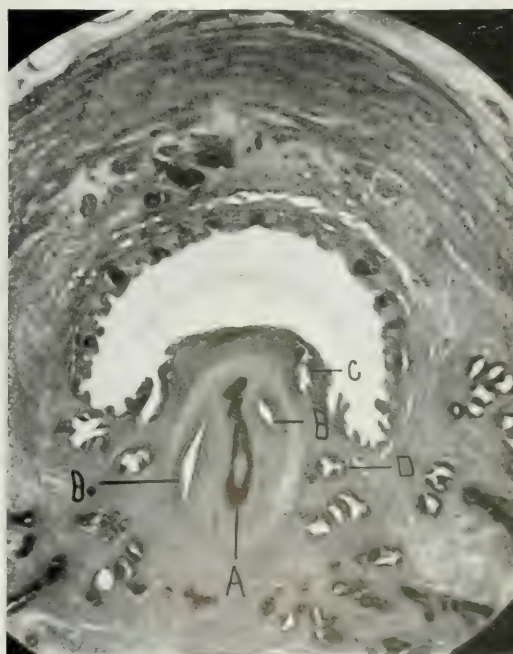


FIG. 10.

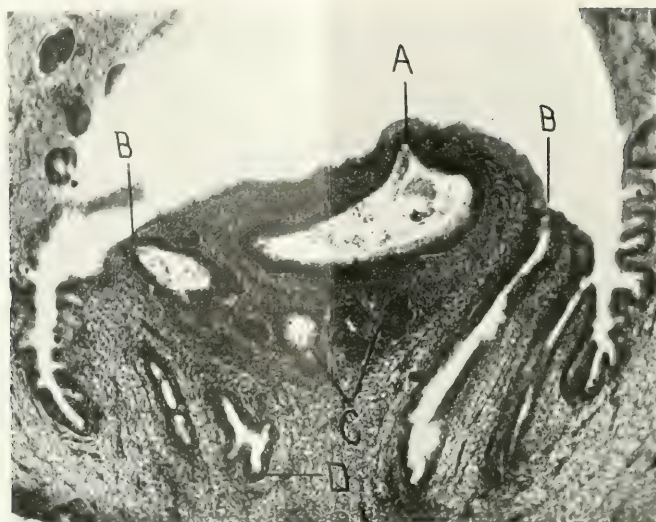


FIG. 12.



FIG. 11.

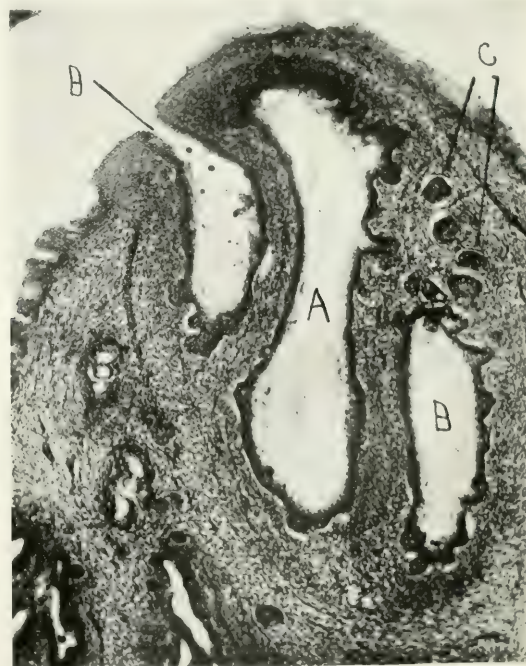


FIG. 13.



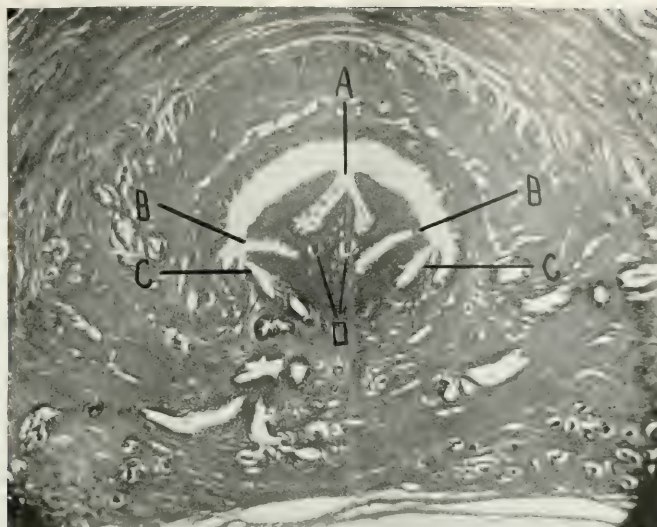


FIG. 14.

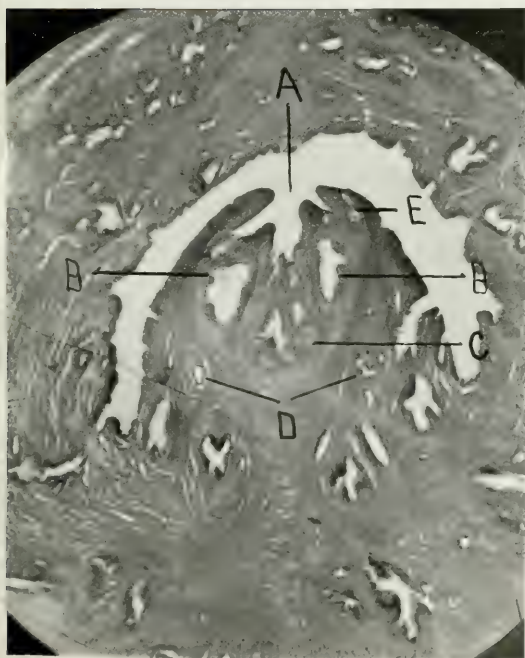


FIG. 15.

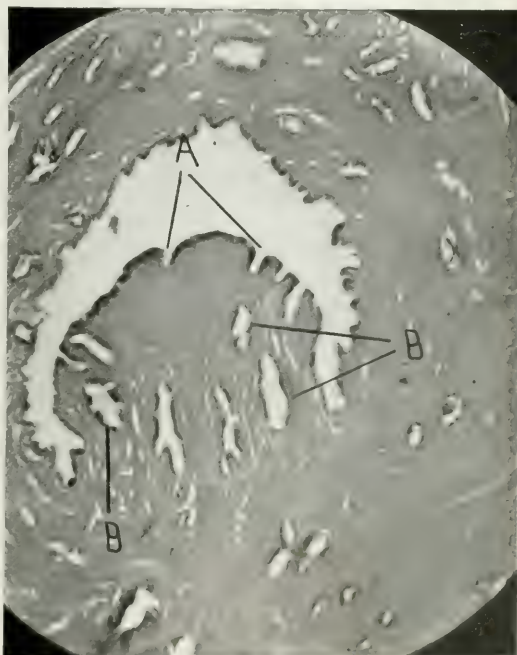


FIG. 16.





FIG. 2

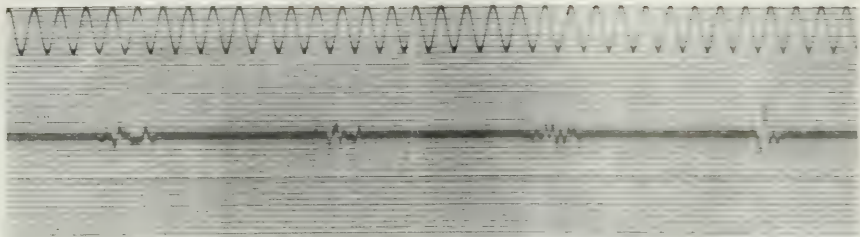


FIG. 3

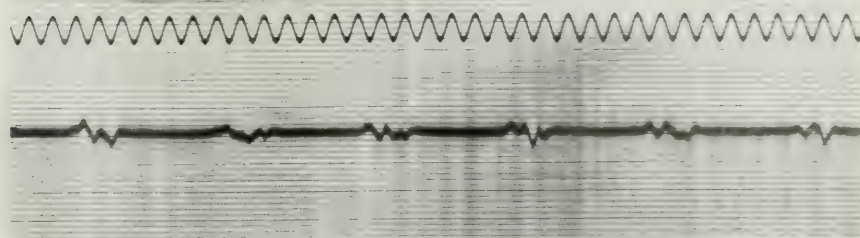


FIG. 4

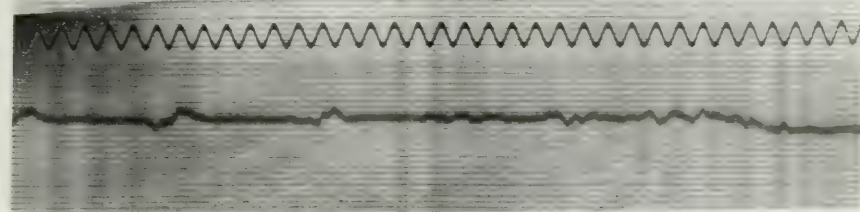


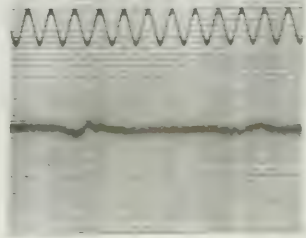
FIG. 5



FIG. 6



FIG. 7







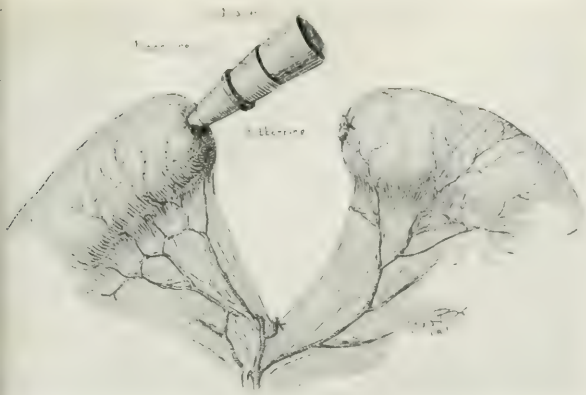


FIG. 1.—The Halsted bulkhead suture. One of the ends of the divided intestine is being invaginated by the wooden mandrel which carries the paper cone.

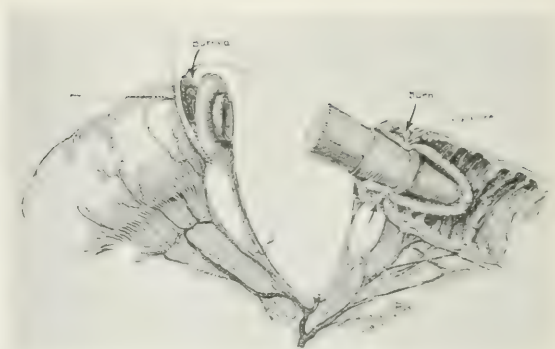


FIG. 2.—The Halsted bulkhead suture. On one side the intestine has been partially burned through by the cautery knife.

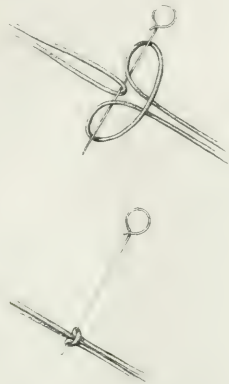


FIG. 5.—The wire-release ligature. Having invaginated the end of the intestine with the fibrin bolus (instead of the wooden mandrel carrying a paper cone—see Fig. 2) the operator ties the wire-release ligature securely about the bowel to anchor the bulkhead.

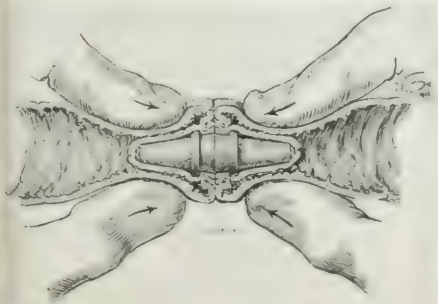


FIG. 3.—The Halsted bulkhead suture. The ends of the intestine and the paper cones, having been divided with the cautery knife, are apposed, the invagination bulkheads being held firmly in place by the encircling ligatures.

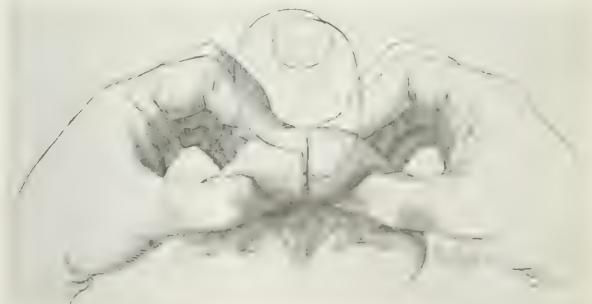


FIG. 4.—The Halsted bulkhead suture. The fingers of an assistant are producing a slight additional invagination to eliminate the danger of engaging the invaginated bowel in the suture.

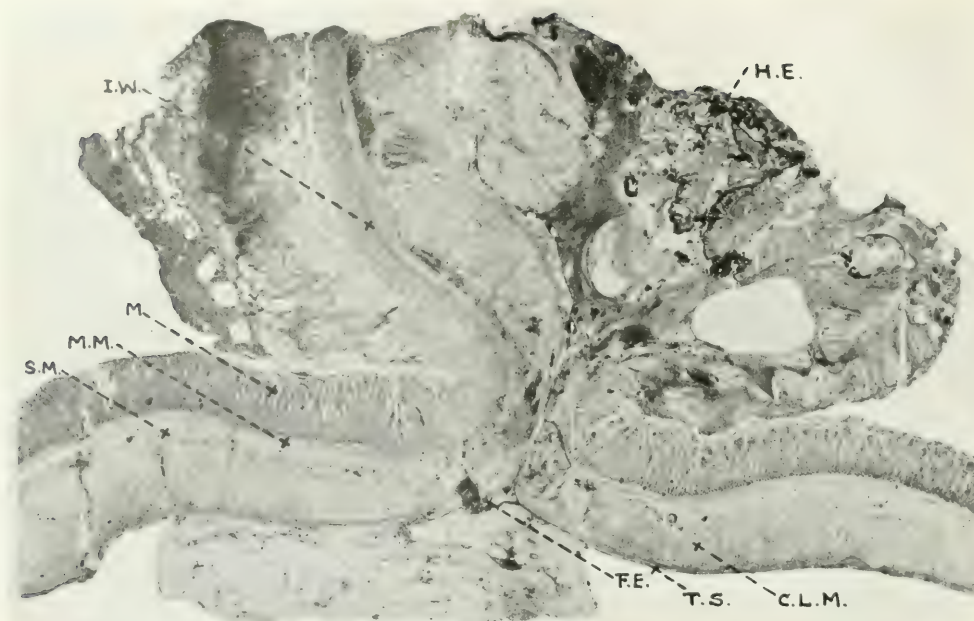


FIG. 6.—Section of end-to-end intestinal anastomosis. Modified bulkhead method (wire-release ligature and fibrin bolus) of 48 hours. I. W., invaginated bowel wall; H. E., hemorrhagic exudate; M., mucosa; M. M., muscularis mucosae; C. L. M., circular and longitudinal muscle layers; T. S., tunica serosa; F. E., fibrinoplastic exudate.



FIG. 7.—Bulkhead suture (wire-release ligature and fibrin bolus) of 72 hours. S., stitch; N. I., necrosis of intumescence

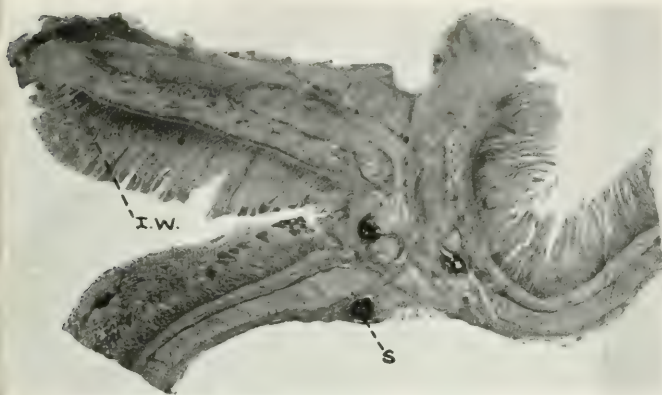


FIG. 8.—Bulkhead suture (wire-release ligature and fibrin bolus) of 5 days. S., stitch; I. W., unusually well-nourished intumescence.

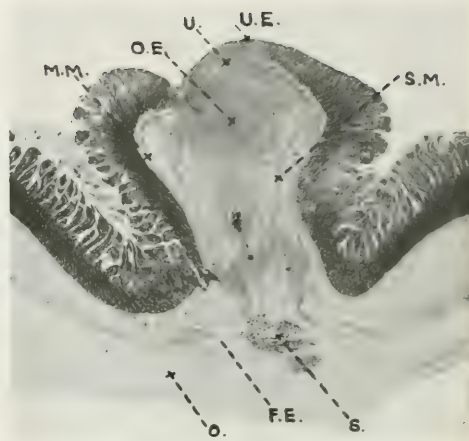


FIG. 9.—Bulkhead suture (wire-release ligature and fibrin bolus) of 7 days. U., ulcer; O. E., organizing exudate; U. E., undifferentiated epithelium; M. M., muscularis mucosae; S. M., submucosa; F. E., organizing fibrinoplastic exudate; O., omentum; S., stitch.

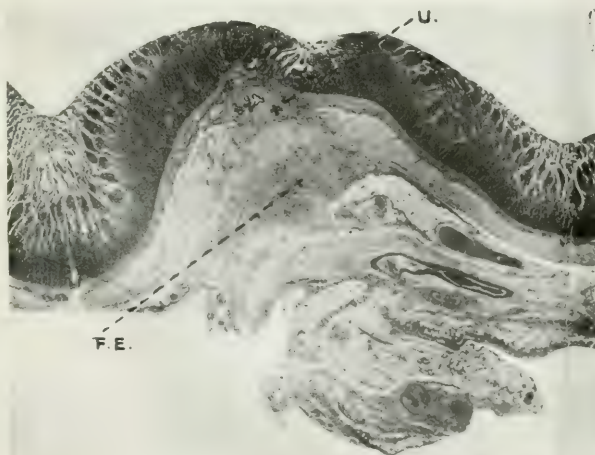


FIG. 11.—Bulkhead suture (wire-release ligature and fibrin bolus) of 24 days. U., ulcer capped by moderately high epithelium; F. E., scar tissue between muscle coats still showing many leucocytes; intumescence almost disappeared.

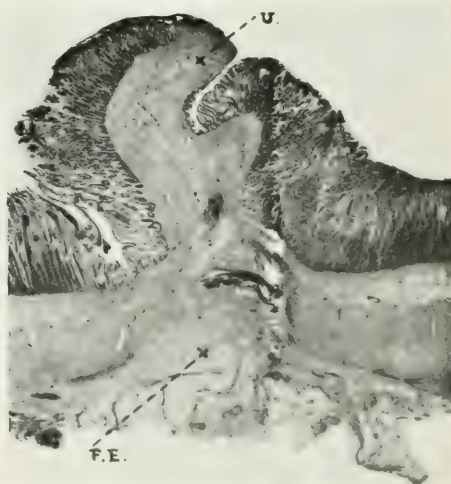


FIG. 10.—Bulkhead suture (wire-release ligature and fibrin bolus) of 14 days. U., ulcer covered by low, undifferentiated epithelium; F. E., organized exudate between muscle coats.





FIG. 12.—Bulkhead suture (wire-release ligature and fibrin bolus) of 41 days. L. U., line of union of muscle coats; Sc., wide scar between muscle coats due to "straightening of the suture."

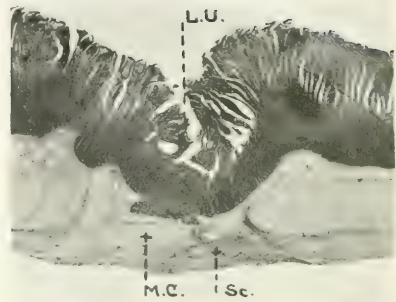


FIG. 13.—Bulkhead suture (wire-release ligature and fibrin bolus) of 63 days. L. U., line of union of mucous coats; M. C., muscle coats more closely approximated; Sc., scar tissue disappearing.

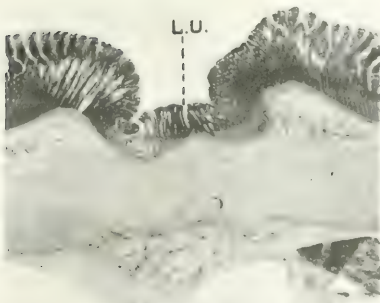
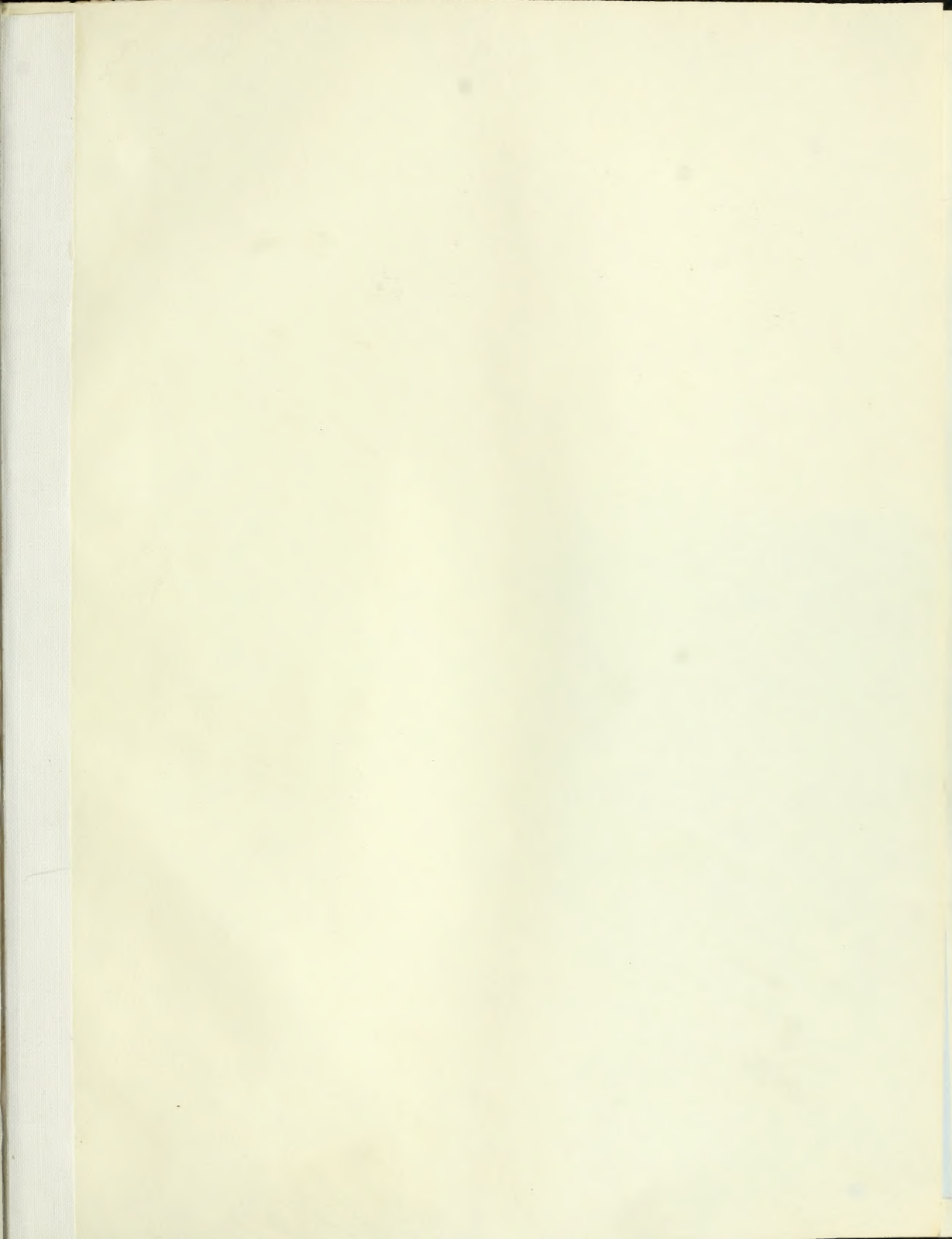


FIG. 14.—Bulkhead suture (wire-release ligature and fibrin bolus) of 79 days. L. U., line of union of the coats.



FIG. 15.—Bulkhead suture (wire-release ligature and fibrin bolus) of 97 days. L. U., line of union of the coats. The dark stippling at A is due to sublimate precipitate.







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